AMERICAN HEART JOURNAL

For the Study of the CIRCULATION

©Am. Ht. Assn.

PUBLISHED MONTHLY
Under the Editorial Direction of
THE AMERICAN HEART ASSOCIATION

Fred M. Smith.....Editor-in-Chief

Associate Editors

Hugh McCulloch
Horace M. Korns
Edgar V. Allen

Editorial Board

CLAUDE S. BECK
NORMAN E. FREEMAN
HARRY GOLDBLATT
GEORGE HERRMANN
WILLIAM J. KERR
ROBERT L. LEVY
H. M. MARVIN
JONATHAN C. MEAKINS
ROY W. SCOTT
ISAAC STARR
J. MURRAY STEELE
PAUL D. WHITE
FRANK N. WILSON
CHARLES C. WOLFERTH
IRVING S. WRIGHT

VOLUME 27
JANUARY—JUNE, 1944

ST. LOUIS
THE C. V. MOSBY COMPANY
1944

COPYRIGHT 1944, BY THE C. V. MOSBY COMPANY

(All rights reserved)

Printed in the
United States of America

Press of
The C. V. Mosby Company
St. Louis

FEB 4 1944

Vol. 27 JANUARY, 1944 No. 1

AMERICAN HEART JOURNAL

For the Study of the CIRCULATION

Medical Library

FRED M. SMITH----------Editor-in-Chief

Associate Editors

HUGH McCULLOCH
HORACE M. KORNS
EDGAR V. ALLEN

EDITORIAL BOARD

CLAUDE S. BECK
NORMAN E. FREEMAN
HARRY GOLDBLATT
GEORGE HERRMANN
WILLIAM J. KERR
ROBERT L. LEVY
H. M. MARVIN
JONATHAN C. MEAKINS
ROY W. SCOTT
ISAAC STARR
J. MURRAY STEELE
PAUL D. WHITE
FRANK N. WILSON
CHARLES C. WOLFERTH
IRVING S. WRIGHT

Published Monthly Under the Editorial Direction of The American Heart Association

Published and Copyrighted 1944 by The C. V. Mosby Company, St. Louis, U. S. A.

Contents on Inside Cover

American Heart Journal

For the Study of the Circulation

CONTENTS FOR JANUARY, 1944

Original Communications

An Intimate Account of My Early Experience With Coronary Thrombosis. James B. Herrick, M.D., Chicago, Ill. ---------- 1

The Precordial Electrocardiogram. Frank N. Wilson, M.D., Franklin D. Johnston, M.D., Francis F. Rosenbaum, M.D., Herman Erlanger, M.D., Charles E. Kossmann, M.D., Hans Hecht, M.D., Nelson Cotrim, M.D., Roberto Menezes de Oliveira, M.D., Roberto Scarsi, M.D., and Paul S. Barker, M.D. ---------- 19

Toxic Reactions to the Intravenous Injection of Mercurial Diuretics. Jack Wexler, M.D., and Laurence B. Ellis, M.D., Boston, Mass. 86

Experiments With Calculated Therapeutic and Toxic Doses of Digitalis. V. Comparative Effects of Toxic Doses of Digitalis and of Pitressin on the Electrocardiogram, Heart, and Brain. William H. Dearing, M.D., Arlie R. Barnes, M.D., and Hiram E. Essex, Ph.D., Rochester, Minn. ---------- 96

Experiments With Calculated Therapeutic and Toxic Doses of Digitalis. VI. Comparative Effects of Toxic Doses of Digitalis and of Prolonged Deprivation of Oxygen on the Electrocardiogram, Heart, and Brain. William H. Dearing, M.D., Arlie R. Barnes, M.D., and Hiram E. Essex, Ph.D., Rochester, Minn. ---------- 108

Clinical Report

Intrapericardial Aneurysm Caused by Congenital Syphilis. C. Dominguez, R. F. Schärer, and E. R. Pietrafesa, Buenos Aires, Argentina ---------- 121

Abstracts and Reviews

Selected Abstracts ---------- 129

Book Review ---------- 143

American Heart Association, Inc. ---------- 144

Vol. 27, No. 1, January, 1944. American Heart Journal is published monthly by The C. V. Mosby Company, 3523 Pine Blvd., St. Louis, Mo. Subscription Price: United States, its Possessions, Pan-American Countries, $10.00; Canada, $11.50 (Canadian Currency); Foreign, $11.00. Entered as Second-Class Matter at Post Office at St. Louis, Mo., under Act of March 3, 1879. Printed in the U. S. A.

Medical
Wahs

American Heart Journal

VOL. 27 JANUARY, 1944 NO. 1

Original Communications

AN INTIMATE ACCOUNT OF MY EARLY EXPERIENCE WITH CORONARY THROMBOSIS

JAMES B. HERRICK, M.D.
CHICAGO, ILL.

FROM time to time for twenty-five years or more it has been suggested to me that I write a history of the coronary artery and its diseases. Among those who have most strongly urged this have been Dr. Joseph A. Capps of Chicago, Dr. Frank N. Wilson of Ann Arbor, and Dr. Fred M. Smith of Iowa City. On Dec. 18, 1935, a direct personal appeal was made by Dr. Wilson.

In his letter he said that I was chiefly responsible for impressing upon the medical profession the importance of coronary occlusion. He felt that a small book giving "details that never get into the concise reports written for publication in a medical journal . . . would be of great value."

I replied that I had decided not to write the book. It seemed unwise to do what would lead students and practitioners, who in the future might be seeking information on the subject, to depend upon an abstract, even though it was made by the author himself. It was much better for them to consult the original articles. Moreover, it was doubtful whether today I could accurately depict my mental processes of twenty-five years ago; unconsciously, the ideas of later years would creep in. Besides, there would be no freshness about writing such a book; it would be little more than a repetition of what I had already said. At 74 years of age the task would be onerous and irksome. Nor was I as competent as many others to discuss adequately certain features that were involved, e.g., the electrocardiogram and some physiologic principles. His letter had, however, opened up the whole question as to whether I ought to tell the story of how I "got onto" the clinical features of acute coronary occlusion.

Received for publication Nov. 15, 1943.

In a letter of Jan. 3, 1936, Dr. Wilson urged that "an intimate account of your early experiences with coronary thrombosis would be of the greatest interest both to the present and to future generations." It would, he added, have an historical value. It would help to impress the importance of study of the patient at the bedside, of using eyes, ears, fingers, and of making and preserving careful records of observations. He commented on the fact that my results had been obtained without the help of new instruments of precision or any new method of examination. An article such as he was advising would, he believed, encourage others to make similar studies.

This matter, while not entirely forgotten in the last seven years, has not been taken up earlier for several reasons: concentration on preparing for, and writing, *A Short History of Cardiology;* a long, serious illness; pressure of many other interests that at the time seemed to call for immediate attention; and the attitude of the octogenarian who hesitates to undertake what, to him, appears to be a formidable task. My decision not to write the larger history of the coronary artery and its diseases has not been changed. There are many of the younger group who, more appropriately and more satisfactorily than I, can write such a volume.

The decision to write in accordance with the suggestion in Dr. Wilson's letter, with the purpose of telling how I became aware of the frequent occurrence of acute coronary occlusion and realized the possibility of its clinical recognition, has been reached for several reasons:

1. The earnest solicitation of three friends, Doctors Capps, Wilson, and Smith, on whose good judgment I place much reliance.

2. The importance of the subject. There is truth in what Roy Scott wrote in 1930: "Medical history of the future doubtless will record as one of the important contributions to the past twenty years, the general recognition of coronary thrombosis."

3. D. E. Bedford's statement (*Practitioner,* June, 1933) that "the knowledge that coronary thrombosis is compatible with life and even health and that it can be recognized with certainty in many cases, has come to us in the last twenty years and we owe it largely to the work of American physicians, and," he adds, "especially to Herrick."

4. The interest that has been manifested when I have talked casually of it to friends, and especially that which was shown on two occasions when in an intimate way I spoke to small groups of doctors.

In 1927, in Pasadena, at an impromptu meeting of the "Stanley Black Club" (there were perhaps thirty doctors at the gathering) I told how my curiosity about the subject had been aroused, and recited details of my experience with my first case.

April 12, 1933, I addressed the attending and resident staffs of the Mayo Clinic at Rochester, Minnesota. Particulars of the first three cases with autopsy were gone over. My notes for this off-the-record

talk show that I closed with an expression of the hope that my young hearers would get from it two ideas. The first was that all medicine needs periodic overhauling. We should avoid the paralyzing influence of the dead hand of tradition, should get away from "the habit complex of groove thinking that is so prevalent in medicine."[1] I cited Laubry[2] as saying that the desirability of periodic revision of ideas applied particularly to diseases of the heart. The second lesson was, though some leaders did not agree, that there was still room for sane, careful, bedside observation. Neither the all-time hospital clinician nor the laboratory worker had a just claim to proprietary ownership of productive, healthy doubt and skepticism. There was a place for all types of investigation. The laboratory, the ward, the library should all be regarded as workshops for observation, experiment, and logical thinking. The watchword should be cooperation. Will Mayo told me later that I would never know how much good that talk had done his staff in the way of stimulation and encouragement.

5. In reviews of my *Short History of Cardiology* there are expressions of regret that, while several pages are devoted to an historical résumé showing how coronary thrombosis (a topic to which "the author himself had made many worthy contributions") was for long overlooked, the subject of how it was "put on the map" has not been taken up. When such men as Sir Thomas Lewis, Paul D. White, E. B. Krumbhaar, and the writer of the unsigned review in the London *Lancet*, Feb. 6, 1943, express themselves in this fashion, one must listen seriously and respectfully.

This, then, is my apologia, with that word's triple implication of apology, explanation, and—if necessary—defense, for writing this very intimate and very personal paper.

* * * * *

A few words regarding the character of my work from the time of my graduation from Rush, in 1888, to 1912, the date of my first paper on "Coronary Occlusion," seem to be in order. At the close of my internship in Cook County Hospital, in 1889, I knew that I was not cut out for a surgeon, nor for an obstetrician or gynecologist. Though ophthalmology, dermatology, and neurology held out attractions, my leanings were definitely towards internal medicine. For at least twenty-five years my aim was to be an all-round practitioner, an internist, as one often says nowadays. In the last two decades, much against my will, there has been forced upon me the term "heart specialist."

Yet, in retrospect, I see that even from student and intern days heart disease attracted me. There still remains the memory of my excitement over my first case of angina pectoris. The patient was a simple, intelligent German, whose story of attacks of pain sounded like angina and yet left me hesitating to venture such a diagnosis un-

til, one day as I was making ward rounds, I saw him sitting erect in a chair, pale, the picture of anguish. At my order the nurse rushed for the nitrite of amyl. After a few inhalations, a look of incredulity came over him. As, breathing more freely, he relaxed from his tense attitude, tears came into his eyes, and, with the courtesy of the old-world peasant, he grasped my hand and kissed it. I was almost as incredulous as he; it was too good, too marvelous, to be true.

Then, probably because I early taught physical diagnosis, I became enamored of heart murmurs and other signs of heart disease. There was perhaps a little playing to the gallery of students and interns when one made a diagnosis of mitral stenosis by simple palpation that revealed the presystolic thrill and the sharp pulmonic valve closure; or when, by noting the collapsing or capillary pulse, or the Duroziez phenomena, one recognized aortic regurgitation. At that period I was often called to see a supposed case of typhoid fever, which disease was then prevalent in Chicago. There was real pleasure in demonstrating to the attending doctor that his patient was suffering, not from typhoid, but from a malignant type of endocarditis; in explaining that he should view the condition, not from the standpoint of the mechanics of the valve, but of an infection. The valve was not only a freshly infected, but was an actively infecting, focus.

It is clear to me now that my attitude toward diagnosis in general had much to do with my early recognition of coronary thrombosis. Diagnosis appealed to me very early, even in intern days. An obscure case was a challenge to one's keenness of observation and skill in interpretation. There was a feeling of satisfaction if a diagnosis was shown to be correct; one of disappointment if it was wrong. Chagrin at failure might be tempered by finding that the condition was one that was practically impossible of intra-vitam recognition, or one that was irremediable by drug or surgery, e.g., an inoperable carcinoma. Chagrin was changed to bitter remorse if it was revealed that, through delay in diagnosis, or because of a wrong diagnosis, the opportunity for proper treatment had been lost and a life sacrificed, e.g., as in perforation of the bowel in typhoid fever.

Another proof that, by 1910, I had been a good deal occupied with heart disease is that I had already written several papers about it: "Tricuspid Stenosis" (1897), "Concretio Cordis" (1898), "Healing of Ulcerative Endocarditis" (1902), "Erroneous Notions Concerning Angina Pectoris" (1910). When, therefore, the first case that I recognized as acute coronary occlusion came along, I was pretty familiar with the literature of heart disease and had had quite an extensive clinical experience with it. Moreover, and this seems to me an important feature, I had as a background a knowledge of general medicine. I felt at home in the field of diseases of the lung, stomach, bowel, and kidney; had seen many cases of diabetes, exophthalmic goiter, diseases of the blood,

and infectious diseases; and I had taught these subjects to students, both didactically and clinically. The wise pathologist, when he looks at a stained section for microscopic diagnosis, before turning on the oil immersion lens, uses first the low power. Or he may even do as did Hans Chiari, under whom, in 1894, I studied in Prague: always hold the slide up to the light, and look at it first with the naked eye. The wider field of vision enables him to understand more clearly the relation of parts, an important factor in trying to reach a diagnosis. So, when confronted by a puzzling case, it had become almost second nature to me, after the analogy of the pathologist, first to consider the case in its broader relations, and to think of the heart only after disease in other organs had been with reasonable probability excluded; it was illogical and often disastrous to jump hastily to the conclusion that the heart was at fault.

* * * * *

The history of my first case of acute coronary occlusion is copied, with a few minor changes, from my article, as read before the Association of American Physicians, May 14, 1912.[3]

CASE 1.—*History.*—On Jan. 16, 1910, a man, aged 55 years, supposedly in good health, was seized an hour after a moderately full midnight meal with severe pain in the lower precordial region. He was nauseated, and, believing that something he had just eaten had disagreed with him, he induced vomiting by tickling his throat. The pain continued, however, and his physician was called. He found him cold, nauseated, with small, rapid pulse, and suffering extreme pain. The stomach was washed out and morphine given hypodermically. The pain did not cease until three hours had passed. From this time on, the patient remained in bed, free from pain, but the pulse continued rapid and small, and numerous râles appeared in the chest. When I saw him twelve hours after the painful attack, his mind was clear and calm; moderate cyanosis and mild dyspnea were present. The chest was full of fine and coarse moist râles; there was a running, feeble pulse of 140. The heart tones were very faint and there was a most startling and confusing hyperresonance over the chest, the area of heart dullness being entirely obscured. The abdomen was tympanitic. The urine was scanty, of high specific gravity, and contained a small amount of albumin and a few casts. The temperature was subnormal, later going to 99° F. Occasionally there was nausea, and twice a sudden projectile vomiting of considerable fluid material. This condition remained with slight variations up to the time of his sudden death, fifty-two hours after the onset of the pain, though at one time the râles seemed nearly to have disappeared. A few hours before death the patient described a slight pain in the heart region, but said it did not amount to much. A remarkable circumstance, and one that occasioned surprise in those who saw the patient and who realized from the almost imperceptible pulse and the feeble heart tones how weak the heart must be, was the fact that he frequently indulged in active muscular effort without evident harm. He rolled vigorously from side to side in the bed, sat suddenly bolt upright, or reached out to take things from the table near by; once, feeling a sudden nausea, he jumped out of bed, dodged the nurse, and ran into the

bathroom, where he vomited; and yet he seemed none the worse for these exertions.

Necropsy (Dr. L. Hektoen).—The heart was of normal size. Both coronary arteries were markedly sclerotic, with calcareous districts and narrowing of the lumen. A short distance from its origin the left coronary artery was completely obliterated by a red thrombus that had formed at a point of great narrowing. The wall of the left ventricle showed well-marked areas of yellowish and reddish softening, especially extensive in the interventricular septum. At the very apex the muscle was decidedly softer than elsewhere. The beginning of the aorta showed a few yellowish spots, these areas becoming less marked as the descending part was reached. An acute fibrinous pericardial deposit, which showed no bacteria in smears, was found over the left ventricle. (The pericarditis perhaps explains the slighter pain complained of a few hours before death.) There was marked edema of the lungs. In other respects the anatomic findings were those of health.

A few details are added. The patient was a slender, active man, head of a private banking house. He had taken the midnight meal of a sandwich and a bottle of beer after he and his wife had returned from the theater, in Chicago, to the suburb in which he lived. Twelve hours later, his physician, Dr. L. W. Bremmerman, asked me to see the patient with him. The nature of the persistently rapid, feeble pulse was a puzzling and alarming feature to both of us. We asked help of Dr. Frank Billings. He admitted he did not know the exact cause, but spoke of the possibility of a cardiac accident, such as acute dilatation of the heart. That the accident might be primarily abdominal was considered, and to help rule out some such condition that might call for surgical interference we decided to call in Dr. John B. Murphy.

Dr. Murphy, an intimate friend of the family, quickly responded, and met Dr. Bremmerman and myself. Dr. Billings was not present on this occasion. Dr. Murphy believed that there was no subdiaphragmatic accident, but was much impressed by the hyperresonance of the thorax. Could it be an acute pneumothorax? I felt not, because the resonance was bilateral, râles and breath sounds could be heard on both sides, and, as near as one could make out, there was no dislocation of the heart. The dyspnea was less than one would expect if there were an overwhelming pneumothorax. So threatening was the condition that we called up a son in New York, telling him to hurry home. I shall never forget Dr. Murphy's emphatic way, as, in his rasping voice, he shouted (the long distance connection with New York was not as perfect in those days as now): "No! no! don't wait for the Century tomorrow. Go straight to Mr. ———" (a high New York Central official) "and get a special. What's the matter with you? Get busy, come right away or you'll be too late!"

At the request of the family, Dr. Murphy and I came back in the evening and stayed all night. We were in a big room with twin beds. Murphy, hearing me turn in bed, but not wishing to waken me if I

were asleep, would whisper, "Herrick, are you awake? Say, are you sure about there being no pneumothorax?" A little later, from my bed, also in a stage whisper: "Dr. Murphy, do you think this might be an acute pancreatitis, or possibly a strangulated diaphragmatic hernia?" Neither of us slept much. We got up once or twice during the night to look at the patient.

As recorded in the history, the patient, with little suffering and with little change in condition, lived until about 4 A.M., January 18, when suddenly the heart and breathing stopped. The autopsy by Dr. Hektoen was performed the same day. I was unable to be present. Dr. Hektoen asked me over the telephone what he might expect to find. My reply was, "Look for a clot in the coronary artery. If you don't find that, find a perforated gallbladder or a perforating duodenal ulcer, hemorrhagic pancreatitis, hemorrhage into the adrenals, strangulated hernia, perhaps a diaphragmatic hernia, ruptured pleura, or any other accident you know about." Dr. Hektoen, with the dry humor for which he is well known, with mock courtesy thanked me for giving him such a great variety to choose from. He called me up that evening and said: "The clot was in the coronary artery, all right. But how in God's name did you guess it?" Perhaps guess was the right word. Among my treasured letters is one from Dr. Murphy, who warmly congratulated me on my diagnosis.

As, after more than thirty years, I try to recall the incident, I believe that my ante-mortem diagnosis was reached largely because, in a hurried search for relevant cases, chiefly in textbooks that were in my home library, I was greatly impressed by the case of Panum, which was described by Fraentzel. Panum, after a severe, angina-like attack, had lived fourteen hours. The rapid, feeble pulse had been a striking feature. Autopsy had revealed acute coronary thrombosis. As positive evidence this carried great weight with me because of the similarity of symptoms. On the negative side it seemed justifiable in our case to exclude extracardiac causes for the severe prolonged epigastric pain that had been followed by cardiovascular failure and death. Disease of the gallbladder or perforation of a peptic ulcer seemed unlikely. Rarer conditions, like adrenal hemorrhage, hemorrhagic pancreatitis, and strangulated diaphragmatic hernia were possible, though improbable. While there was no evidence of valvular disease or of enlargement of the heart, and while there was no reason to suspect physical overstrain, the heart seemed to be incriminated. The outstanding feature appeared to be a sudden weakening of the myocardium. Perhaps, after the analogy of thrombosis in cerebral arteries, there had been a thrombotic occlusion of the coronary artery, the nutrient vessel of the heart's muscle.

As, in retrospect, I go over the whole incident again, and try to reconstruct my mental state and the processes of reasoning I went through at that time, I realize that the interpretation appears far simpler after the event than it was in those two hectic days, in which there were many

doubts, many shifts of opinion, many hours of genuinely anxious uncertainty. The old adage about the superiority of hindsight over foresight may well be applied in this instance.

That I did not at once grasp the full significance of the first case is evident from the rather casual reference to it contained in a paper[4] that I read in June, 1910, in the Section on Practice of Medicine of the American Medical Association at the meeting in St. Louis. I said that, in some of the most serious cases of angina pectoris, "there is low blood pressure, indicating perhaps a weakened myocardium. In a man 54 years of age [*sic*] with no general arteriosclerosis, I have seen the rough-walled left coronary plugged in its anterior branch with a thrombus producing sudden excruciating precordial pain. For the fifty hours that the patient lived the heart tones were barely perceptible, and the peripheral pressure extremely low. But in cases in which there is no such acute and extensive myomalacia cordis as was present in this instance, the pressure may be low for a long time and the patient busy about his work, though interrupted at times by the attacks" (of angina pectoris).

Soon after this, however, evidently from further reading and study, I realized more clearly that cases of this type were not rare and that the whole subject was worth more extended observation. This is shown by the fact that in October, 1910, I had seen in consultation a man 65 years of age who had lived seven days from the onset of what, from the typical symptoms, was to my mind an unquestioned case of coronary thrombosis in one who had for some three years been a sufferer from angina of effort. This is recorded as Case 2 in my paper of 1912.

It is evident that, long before May, 1912, when I read my paper at the Association of American Physicians, I had become much surer of my ground, for, in May, 1911, at Des Moines, in the course of an address on "Pain in Disease of the Heart," delivered before the Section on Medicine of the Iowa State Medical Society, I devoted about 1,500 words to acute obstruction of the coronary artery.[5] The views there expressed were based on the first case with autopsy (1910), and five others without autopsy. The views, and largely the language, are those contained in the later paper of May 14, 1912. The concluding paragraph is perhaps worth quoting, as it shows that my ideas at that time were pretty well crystallized, and because it voices the same notions regarding the possibilities and value of noninstrumental diagnosis that are referred to by Frank Wilson in his letter of Jan. 3, 1936. With slight alteration in punctuation and the construction of a sentence, it closed as follows:

"This address, if it accomplishes its aim, will encourage the specialist and the research worker to go forward with the use of the newer instruments and with the investigations by which new facts concerning the heart will come to light. It will also, I trust, encourage the general practitioner to retain some of his old self-confidence and not to lose

faith in his powers of observation and in his ability to analyze subjective symptoms; and still to believe that it is possible by well-established methods of physical diagnosis to understand many of the anatomic, pathologic, and physiologic conditions of this important organ."

Finally, the decision was reached that, after a more thorough study, I would report the case in a special paper. Far-reaching lessons might be drawn from it. A condition previously regarded as merely a pathologic curiosity had been met with in a man who had lived fifty-two hours. In that time symptoms had developed. Might not other similar cases be discovered in the literature, and enough common features be found to enable a clinical picture to be drawn that would make an intravitam diagnosis possible? Moreover, if Panum had lived fourteen hours and my patient fifty-two, might not others live longer? The more I read on the subject and pondered over it, the clearer it became to me that sudden death was by no means the inevitable sequel to the accident. One could find numerous examples in the literature. George Dock, as early as 1896, had recognized and described such cases. Osler had been aware that in some instances of angina pectoris there were thrombotic lesions in the coronary arteries. Obrastzow and Straschesko, though inclined to regard the accident as ushering in an ultimately fatal status anginosus, had, in 1910, drawn a remarkably accurate clinical picture of the condition. If one read between the lines, one could interpret some of Huchard's and Mackenzie's cases as examples of coronary occlusion. And there were others. I gradually became convinced, quoting from my paper of May, 1912, that "one may conclude, therefore, from a consideration of the clinical histories of numerous cases in which there has been careful autopsy control, from animal experiments and from anatomic study, that there is no inherent reason why the stoppage of a large branch of a coronary artery, or even of a main trunk, must of necessity cause sudden death. Rather may it be concluded that while sudden death often does occur, yet at times it is postponed for several hours or even days, and in some instances a complete, i.e., functionally complete, recovery ensues." It was reasonable to assume, also, that milder cases might be met with. So, on the basis of clinical symptoms, I made a tentative grouping that is recorded in my paper and need not be repeated here.

The clinical picture there drawn seems to me, even now, to be fairly accurate. On the whole it contains little that needs deletion or apology; though, if I were to rewrite it today, I would modify my advice as to the use of digitalis as a routine measure in treatment. Many things were overlooked. Since that date countless details have been added by workers in the United States and other countries, and especially since help from the electrocardiograph has been available. No attempt is made here to review these contributions.

One of the strange things about it all, a fact that has caused me regret, is that I overlooked, even in the paper of 1918, so much pertinent material that had been published before. This was partly because of not following more thoroughly certain leads; it was partly because in my reading I was looking for references under the heading "coronary artery." Had I grasped the bibliographic significance of "infarct of the myocardium" I might have unearthed the mine of information contained in René Marie's monograph *L'Infarctus du Myocarde et Ses Conséquences* (1896). To miss the later monograph of M. Sternberg, *Das chronische partielle Herzaneurysma, Anatomie, Klinik, Diagnose* (1914), was a little more excusable though greatly to be regretted. If I remember rightly, it was Joseph T. Wearn, of Cleveland, who, soon after I had read my paper on "Thrombosis of the Coronary Arteries" in 1918, called my attention to these important papers that had escaped my notice.

As is shown in the chapter on the coronary artery, in my *Short History of Cardiology*, the significance of several other writings was not fully realized. Weigert, Huber, Leyden, and others had discussed this condition. I was not the only one, however, who failed to appreciate fully the message contained in their writings; even their fellow countrymen had paid little heed to their words.

It seemed strange to me at the time, it seems strange to me now, that when, in 1912, I read before the Association of American Physicians a paper that seemed to me to contain an important announcement, it fell like a dud. No one, except Emanuel Libman, discussed it or even asked a question. I must have been keyed up to a high pitch, for I recall my eagerness to have the article published promptly; I feared someone else might jump into print ahead of me. My anxiety about priority was groundless. Even after its publication in the *Journal of the American Medical Association*, in December, 1912, it aroused no more comment than it did when it had been read six months before. No really live interest in the topic was manifested until the second paper, on "Thrombosis of the Coronary Arteries," was read before the Association in 1918. This contained reports on two other patients, with the autopsy findings. It contained, besides, a record of Dr. Fred M. Smith's laboratory experiments on dogs, with lantern slides of electrocardiograms and pathologic specimens. In those days, and it is often true today, a lantern slide or a graph, or an experiment on a dog in a laboratory, attracted greater attention than mere observations made at the bedside on human beings.

It is surprising how easy it is, as Isaiah noted long ago (Isaiah 42:20), to hear but not understand, to see but not really observe. We are all human; we have all erred in this respect. At times I wondered why my early paper had attracted no attention; why my Des Moines address had apparently fallen on deaf ears. Then, too, in 1917, at the New

York meeting of the American Medical Association, in the Section on Medicine, I had read a paper on "Angina Pectoris" that had been written by Frank Nuzum and myself.[6] Its reception, when printed, as when read, seemed to me strange. Comments were restricted almost entirely to our statistics and to the more well-known symptoms. That we had described with emphasis the type of angina associated with coronary thrombosis attracted no attention.

By the end of 1910, and especially after 1911, when I read the paper in Des Moines, I began consciously to do what I called missionary work, preaching the gospel of the pathology and clinical symptoms of acute coronary obstruction. In lectures to students, in clinics, in consultations with physicians and in talks before medical societies in Chicago and elsewhere, I talked coronary occlusion almost ad nauseam. A few listened attentively, more, incredulously, the majority, indifferently. I recall an informal talk before a meeting of Western Surgeons in the Rush amphitheater, in which I stressed the resemblance of the accident to acute abdominal surgical conditions. I can still see the quizzical look on Charlie Mayo's face as, from a front seat, he listened to, but was evidently not converted by, my sermon. About a year later, however, a well-known Chicago surgeon called me by telephone and said he had just been asked to go to Iowa to operate on a patient with gallstones. The history of the case, as related to him by the attending doctor, called to mind, he said, something he had heard me refer to in my talk to the surgeons. Had I any reprints of any article on the subject that I could rush to him? I furnished the reprint. Two days later he called me up and said the case in Iowa was a "dead ringer of your coronary thrombosis. You certainly saved one chap from an unnecessary, serious operation."

At times I feared I might be overenthusiastic, too readily "believing to be true that which I wished to be true." I often asked Dr. Smith and my interns, who shared my enthusiasm, whether I was becoming "nutty." They thought not.

* * * * *

Then, in March, 1914, there came along the second case in which there was an autopsy. This strengthened my belief that the accident was of not infrequent occurrence and that it could be diagnosed. The case is briefly reported in the paper on "Coronary Thrombosis" read in May, 1918.[7]

CASE 2.—A man, aged 62 years, while walking on the boardwalk at Atlantic City, was seized with a terribly severe pain in the lower precordia. He was helped to the hotel, but refused to call a physician while in Atlantic City or for the next two days while in New York, for, as he said, he knew from the severity of the initial pain, the great weakness, and difficult breathing that he would be ordered to a hospital, and he wished to get to his home in Chicago for his illness and, as he feared, his death. He lived over two weeks from the onset of the attack, dying

March 22, 1914. His heart when he reached Chicago was dilated, weak, and somewhat rapid. His blood pressure became progressively lower. There were dyspnea, cyanosis, marked edema of the legs, and albuminuria. Death was as in ordinary cardiac failure. Necropsy revealed recent plugging by a thrombus of the descending branch of the left coronary artery, with softening of the heart muscle at the left apex and lower interventricular septum.

This patient was under the care of Dr. Joseph A. Capps, who represented the family physician, Dr. Frank Billings, who was abroad at the time. The patient had been in such distress while on the journey from New York to Chicago that he had asked his friend, Dr. L. L. McArthur, whom he met on the train, to help him. Dr. McArthur, I believe, gave him a hypodermic of morphine and assisted in his care after he reached Chicago. I saw the patient several times with Dr. Capps and Dr. McArthur. The diagnosis of acute coronary occlusion seemed warranted. There was no reason for suspecting preceding heart trouble, as the man shortly before had been carefully examined by Dr. Billings and pronounced in good health, with nothing abnormal as to heart, blood pressure, urine, etc. The sudden knock-out blow, with its prolonged pain, breakdown of heart's function, and with increasing congestive failure in spite of rest and other measures that were employed, made it almost certain that the coronary artery was occluded. So distressing was the dyspnea, so pronounced the venous distention, and so marked the cyanosis, that venesection was deemed advisable and was performed by Dr. McArthur a day or two before the patient died. The autopsy by Dr. Hektoen showed, as in the first case I had seen, that the sclerosis was limited almost entirely to the coronary artery. In the first case, while aortic sclerosis was not marked, there was more than in this second case, and the coronary artery was more involved.*

* * * * *

It is to be noted that, in the study of the cases reported before 1918, there had been no help from the electrocardiograph. Between 1910 and 1918 a Cambridge instrument was installed in Presbyterian Hospi-

*In a letter dated May 29, 1943, Dr. Capps, in answer to my request for criticism of the first draft of the manuscript of this paper, reminded me that I had failed to refer to the finding of bacteria in the heart of this patient. "You may recall," Dr. Capps writes, "that the patient was suffering from a cold at the time of onset, and that Dr. Hektoen found, in sections of the coronary artery, cocci overlying an atheromatous patch, and described layer after layer of fibrin deposited on the nucleus of bacteria. And," Dr. Capps adds, "you refer to another case of thrombosis in which infection was a factor. I thought this might be a little further emphasized as a causative factor in a certain group of cases."

In my reply I thanked Dr. Capps for so properly calling to mind what I had entirely forgotten. It was true, I agreed, that not infrequently bacteria have been found at necropsy on patients dying of acute coronary thrombosis. It was also true that a time relation between an existing focus of infection and the clinical symptoms of the "heart attack" has often been noted. But I was not thoroughly convinced that in all, or even a majority, of these cases, the coronary lesion was due to infection from such a focus. It is so easy to find a focus when it is being looked for; few persons are without one or two at least. And we should not apply too readily the old, false *post hoc ergo propter hoc* argument. There is the possibility of mere accidental association. Also, the bacteria in the case of this patient might have been due to a complicating or a terminal infection. "Yet, you may be right," I added, "I know that Dick, Irons, and others have been impressed by the view that acute coronary thrombosis is often (some say it is the rule) due to an infectious process that may be in some remote focus: tonsil, teeth, gallbladder, appendix, or bronchi."

tal, Chicago, through the generosity of Madam Cyrus H. McCormick. Through other funds contributed by her and the late Richard T. Crane, Jr., research was made possible. At this time, also, I installed an instrument in my office. Dr. Smith, after some preliminary study of the anatomy of coronary arteries in dog and man, and their anastomoses, began his pioneer experiments in ligating the coronaries in dogs, with electrocardiographic studies. This work, in which he was aided by Dr. Edwin M. Miller who did the preliminary surgical operations, was done in the basement of the Hospital. As the animal cages were kept across the street in the Rush laboratory building, much arduous transfer of animals back and forth to the electrocardiographic room was necessary. The unremitting zeal and enthusiasm of Dr. Smith deserve highest praise. At first I set his problems for him, with suggestions as to technique. I had to hold him down a little. Soon, however, he came to me asking my advice about some new plan. A little later, he came to me not for advice, but to announce what he was going to do or had already done; he had gotten away from me, was ahead of me. His results, largely incorporated in his important paper[8] of 1918, as well as in later articles, are well known to students of heart disease.

* * * * *

It became evident from Dr. Smith's investigations that a fairly constant change in the electrocardiogram was brought about by ligation of coronary arteries in the dog, so that one could predict with reasonable certainty the alteration that would appear in the tracing after experimental stopping of circulation in particular branches. We were now on the alert to see if we could utilize this knowledge in the case of some human being whose symptoms suggested acute coronary obstruction. Might it be possible to localize a lesion in the coronary system with an accuracy comparable to that with which one locates obstructing lesions in the cerebral arteries?

The long-looked-for patient came into my office May 3, 1917, at which time I happened to be absent from the city. The late Dr. James R. Greer, my office assistant at that time, obtained the history, took an electrocardiogram, and ventured a diagnosis of acute coronary obstruction, in which diagnosis Dr. Smith concurred. On my return to the city a few days later, I joined in the excitement aroused by the incident and agreed with Dr. Greer and Dr. Smith that this diagnosis was correct, because of the history and striking resemblance of the electrocardiogram to some of those in Dr. Smith's dogs.

The patient, a physician, 37 years of age, an ex-intern of our Presbyterian Hospital, who had never suffered from angina pectoris, had no acute or chronic infection so far as he knew, and who regarded himself as free from cardiovascular and renal disease, twenty days before had been seized, while in this seemingly good health, with a sudden, excruciating pain in the lower sternal region, which pain radiated to the

arms and to the epigastrium. He was profoundly shocked, very weak and nauseated, the skin cold and clammy, the pulse rapid and thready. His colleagues who saw him thought he would die in a very short time. Morphine, ¾ grain, was necessary to control the pain. After a time he rallied, and in about fifteen days was able to be about and even tried to do some professional work. But in a few days his weakness, precordial distress on exertion, dyspnea, and irregular, rapid, and small pulse caused him to give up. He rested, again improved, and came to Chicago. Rest and small doses of digitalis were ordered. On May 31, 1917, he returned for a checkup, and the condition seemed better. The summer vacation was spent on an island in Lake Michigan, where there was considerable violation of the injunction as to quiet and digitalis, the patient not only eating very heartily, but not infrequently going on strenuous walks, fishing and hunting trips, even though precordial pain, occasional attacks of dyspnea, and cardiac irregularity gave warning that the heart was far from normal. From an unduly severe strain of this sort he suffered for several days with dyspnea and arrhythmia; he contracted an infectious bronchitis and hastened to Chicago, where, in a deplorable condition, he went under my care in the Presbyterian Hospital, Sept. 26, 1917. The dyspnea and cyanosis were marked; he was sleepless and had Cheyne-Stokes breathing; the temperature rose to 102° F. The blood pressure was not high, the heart was slightly enlarged to the left, and there was a faint systolic murmur at the apex. After four days he developed signs of pneumonia; the respiration rose to 32 and the temperature to 106° F. There were bloody and rusty sputum, marked albuminuria, and leucocytosis. He became delirious, and just as a distinct drop in temperature and a clearing of the mind made one wonder if recovery after all might be a possibility, he died suddenly. Necropsy, on October 8, by Dr. Thatcher, of Presbyterian Hospital, disclosed pneumonia of the lower lobe of the right lung and several infarcts in other portions of the same lung.

The heart weighed 415 grams. The enlargement involved both right and left sides. The external surface was fairly normal in appearance, with the exception of a pale, depressed area 4 cm. in diameter, midway between the base and apex of the left ventricle, and a smaller, similar area on the lateral surface close to the apex. The wall of the left ventricle near the apex and the interventricular septum were thin and of gristly consistency, cutting with marked resistance. The endocardium of the left ventricle had a pale, mottled appearance, especially marked over the lower three-fourths of the septum and the papillary muscles. The papillary muscles were smooth, contracted, and firm, these changes being particularly marked in the anterior muscle. The greater extent of the fibrous changes in the endocardial and subendocardial tissues, as compared with those on the external surface of the heart, was striking. The left coronary artery contained an organized thrombus in the ramus descendens anterior, 3 cm. from its origin. Also, the first descending branch of the circumflex was occluded 1.5 cm. from its origin by a fresher thrombus. The coronary arteries showed sclerotic plaques scattered throughout most of their course, these spots varying in size from 0.5 to 2 mm. in diameter. The aortic leaflets were thickened. There were a few sclerotic areas in the suprasigmoid area of the aorta. These were not regarded as syphilitic. It may be added that no history or stigmata of syphilis were noted during life, and that the Wassermann test on the blood had been negative.

This case made a profound impression on all of us. It seemed to furnish incontestable proof that the thesis we had so long been harping on was correct; that acute coronary thrombotic occlusion was not rare; that patients might live for many days after the accident; that in a large proportion of cases the clinical picture was typical enough to permit an intra-vitam diagnosis. More than that, the electrocardiogram not only aided materially in diagnosis, but offered hope that it might reveal the location of the resulting myocardial damage, and, in a measure, its extent, and thus be helpful in the way of prognosis and treatment. These facts were presented in my paper that was read before the Association of American Physicians in May, 1918. The similarity between the electrocardiograms of Dr. Smith's dogs soon after ligation and that of the patient at his first visit, when he was fairly comfortable and able to be about, was striking. No less striking were the tracings made on dogs thirty-four days after ligation of the ramus circumflexus sinister and that taken of the patient 178 days after his illness, when he was in the deplorable condition during his stay in the Hospital. The low amplitude and the widened QRS curves, with other abnormalities, were startlingly alike. These were shown in my paper, and also in Dr. Smith's article, published in the *Archives of Internal Medicine,* June, 1918.

An interesting episode may be mentioned, as showing the attitude of mind of even excellent men at that time. My patient, the doctor, after his first interview with me, went to make a social and semiprofessional visit on a prominent colleague in a large western city. When my diagnosis of coronary thrombosis was mentioned, the colleague emphatically said that neither Dr. Herrick nor any one else was justified in making such a diagnosis except on the autopsy table. The attempt was ridiculous because it was impossible. The instructive and pathetic sequel to this is that, some ten or twelve years later, this same physician called me by telephone and in a feeble voice and in evident alarm told me he had just had an attack of coronary thrombosis, and what would I advise? He would send the electrocardiograms to me at once. Two or three years later a recurrent attack and a necropsy showed that his intra-vitam diagnosis had been correct.

In reaching conclusions regarding this subject I tried to be conservative. To this end the cases that weighed the heaviest were those with necropsy examination. A British writer (the reference has escaped me) some time after interest in coronary occlusion had begun to appear in England, wrote in a journal that the American physician had a great advantage over the British, as in the United States autopsies in public hospitals were far more readily obtained than in England. He did not realize that in the first two cases the post-mortem examinations had been made in the homes of well-to-do patients, and that the third was on a private patient in a hospital that was in no sense a public

institution. That autopsies on private patients are frequently secured if they are asked for is not as widely known as it should be. This statement applies to this country as well as to Great Britain.

* * * * *

On March 28, 1918, a meeting of the Institute of Medicine of Chicago was held at the LaSalle Hotel, at which time the following program was presented:

SYMPOSIUM ON ANGINA PECTORIS

"Angina Pectoris; Personal Experiences of One of Our Members," by E. Fletcher Ingals; read by Ludvig Hektoen
"Pathology of Angina," by Edwin R. LeCount
"Coronary Thrombosis in Relation to Angina," by James B. Herrick
"Clifford Allbutt's Views in Regard to the Etiology of Angina," by Robert H. Babcock

The paper of Dr. Ingals was read by Dr. Hektoen because the author himself was too ill to be present. Dr. Ingals' discussion of angina was based on his experience with the condition in his practice. He described in detail the case of "Dr. X," who, as was generally known, was Dr. Ingals himself.

Dr. LeCount's paper was based on a careful study of "some sixty deaths from difficulties with the circulation of blood in the coronary arteries or with lesions generally regarded as caused by such difficulty. These are in two groups: thirty-four deaths from fibrous myocarditis with sclerosis of the coronary arteries, and twenty-six of more or less acute occlusion."

Dr. LeCount, as physician to the Coroner's office, had had an unusual experience with sudden and unexplained deaths, the "coroner's cases" that for medicolegal reasons require a postmortem examination. He had utilized the opportunity afforded him to make a scientific study of these cases, the results of which he embodied in this important contribution.

In my remarks I epitomized my views on the relation of coronary disease to angina, and discussed coronary occlusion and its clinical features. I repeated much of what had been stated in my 1912 paper, expressing views that, with minor differences, agreed with those of Dr. LeCount. Lantern slides were shown, illustrating the results of Dr. Smith's experimental work. The arguments I advanced and even the wording were much the same as those presented a few weeks later at Atlantic City.

Dr. Babcock spoke at length concerning Sir Clifford Allbutt's theory of angina pectoris, which he was strongly inclined to endorse.

On April 30, 1918, a little more than four weeks after his paper had been read, Dr. Ingals died. A little later, Dr. LeCount, in his report of the necropsy he had made on the body of Dr. Ingals, commented that he found nothing in this examination to support the position of Dr.

Ingals in his adherence to the aortic theory of angina pectoris that had been advanced by Sir Clifford Allbutt.

The papers on angina and coronary disease were published in the *Proceedings of the Institute of Medicine* **2**: 65, 1918. An abstract is also found in the *Journal of the American Medical Association* **70**: 974, 1918. Dr. LeCount's paper, "Angina Pectoris: Report of a Post-Mortem Examination," is in the same volume of the 1918 *Proceedings of the Institute of Medicine*, page 77.

These papers apparently attracted little attention. The explanation is probably that the subject was not at that time one in which the profession was particularly interested. Perhaps also the fact that the Institute of Medicine was young, and its *Proceedings* had a very limited circulation, may be a partial explanation.

It has been a matter of personal regret that I failed to insert in my paper on "Thrombosis of the Coronary Arteries"[7] that I read May 8, 1918, before the Association of Physicians, a reference to LeCount's work. My paper, however, was already in final typewritten form, already announced—and, as I recall, abstracted—on the program of the Association. The omission of reference to LeCount's work was unintentional; but I learned long afterwards that he felt that he had been undeservedly slighted.

* * * * *

There is surely no need to continue this intimate recital of my personal relations to the subject of disease of the coronary artery. Soon after the second paper on "Thrombosis of the Coronary Arteries" had been read, American physicians at the bedside and in the laboratory took up the work, and there was a veritable flood of articles on this topic. I participated, chiefly on the clinical side, and contributed several papers, in addition to delivering many unrecorded talks before students and groups of practitioners.[9]

Of course, I am responsible for all statements of facts, and their interpretation, that are contained in this paper. The major responsibility, however, for deciding to write and publish now, must rest with my three friends who for so long urged me to put these facts on record.

REFERENCES

1. McCarthy, J. T., and Kramer, S. E.: A Consideration of the Malignant Prostate and Associated Obstructive Manifestations, Am. J. Surg. **19**: 214, 1933.
2. Laubry: In Preface to Poumailloux's Le Puls Alternans, Paris, 1930, Masson & Cie, p. 5.
3. Herrick, James B.: Clinical Features of Sudden Obstruction of the Coronary Arteries, J. A. M. A. **59**: 2015, 1912. Also, Tr. A. Am. Physicians **27**: 100, 1912.
4. Herrick, James B.: Certain Popular but Erroneous Notions Concerning Angina Pectoris, J. A. M. A. **50**: 1423, 1910.
5. Herrick, James B.: Pain in Disease of the Heart, J. Iowa M. Soc. **1**: 149, 1911.
6. Herrick, James B., and Nuzum, Frank R.: Angina Pectoris, Clinical Experience With Two Hundred Cases, J. A. M. A. **70**: 67, 1918.

7. Herrick, James B.: Thrombosis of the Coronary Arteries, J. A. M. A. **72**: 387, 1919. Also, Tr. A. Am. Physicians **33**: 408, 1918.
8. Smith, F. M.: The Ligation of Coronary Arteries With Electrocardiographic Study, Arch. Int. Med. **22**: 8, 1918.
9. Some of these are here listed:
   a. Clinical Recognition of Coronary Thrombosis. Weekly Roster and Medical Digest, Philadelphia County Med. Soc. **20**: 13, 1925.
   b. Combination of Angina Pectoris and Severe Anemia; Am. Heart J. **2**: 351, 1927. Also in Tr. A. Am. Physicians **42**: 23, 1927.
   c. Atypical Features of Acute Coronary Occlusion, Ann. Int. Med. **3**: 105, 1929.
   d. Some Unsolved Problems Connected With Acute Obstruction of the Coronary Artery; Am Heart J. **4**: 633, 1929. Also in Tr. A. Am. Physicians **44**: 13, 1929.
   e. The Coronary Artery in Health and Disease, Harvey Lectures, pp. 129-151, 1930-31.
   f. Atypical Features of Coronary Occlusion, Proc. California Acad. Med. **2**: 69, 1931-32.
   g. On Mistaking Other Diseases for Acute Coronary Thrombosis; Ann. Int. Med. **11**: 2079, 1938.
   h. Robert Adams, Surgeon, and His Contribution to Cardiology; Ann. M. Hist. **1**: 45, 1939.

THE PRECORDIAL ELECTROCARDIOGRAM

FRANK N. WILSON, M.D., FRANKLIN D. JOHNSTON, M.D.,
FRANCIS F. ROSENBAUM, M.D., HERMAN ERLANGER, M.D.,
CHARLES E. KOSSMANN, M.D., HANS HECHT, M.D., NELSON COTRIM, M.D.,
ROBERTO MENEZES DE OLIVEIRA, M.D., ROBERTO SCARSI, M.D.,
AND PAUL S. BARKER, M.D.

INTRODUCTION.—Considerable progress has been made in the standardization of precordial leads, but there is still a great diversity of opinion as to how many leads of this kind should be taken, as to what precordial points should be explored, and as to the proper location for the remote or reference electrode. The multiplicity of leads still in use and still being recommended is the source of much confusion and continues to retard progress in the setting up of adequate normal standards and satisfactory diagnostic criteria applicable to the interpretation of the precordial electrocardiogram. It is not, therefore, surprising that there has been a persistent demand that a single standard method for taking precordial leads be established. Unfortunately, it is not easy to meet this demand for there is no generally accepted method for determining which leads are likely to prove most and which least useful, and there are very great differences of opinion as to whether the decisions required should be made on empirical grounds alone, or, if not, as to what general principles should be taken into consideration.

It seems to us that it would be less difficult to solve this problem if there were a more widespread and clearer understanding of the nature of precordial leads, the relations between them and leads of other kinds, the considerations which led to their use, the advantages which have made them popular, and the purposes which they may be expected to serve. We propose, therefore, to discuss the precordial and other special leads which we have used with much satisfaction over a long period. We want to emphasize the principles upon which they are based and to call attention to the kind of information that may be obtained by their use in cases of bundle branch block, ventricular hypertrophy, and myocardial infarction. It is in these conditions particularly that the standard limb leads have been found inadequate.

It is true that much of our present knowledge of the human electrocardiogram has been gained by the correlation of electrocardiographic data and clinical or post-mortem observations. Nevertheless, electro-

From the Department of Internal Medicine, University of Michigan Medical School.

Much of the work upon which this article is based was done with the aid of a grant from the Horace H. Rackham School of Graduate Studies.

This material was presented by Frank N. Wilson at the fifty-third annual meeting of the Association of Life Insurance Medical Directors of America held Oct. 21 and 22, 1942, and has been published in the Transactions of that Association (Vol. xxix, pp. 154-251).

Received for publication Oct. 16, 1943.

cardiography can hardly be considered a purely empirical science. Its physical and physiological foundations rest upon a large body of critical experimentation dictated by well-constructed hypotheses. These foundations were laid, and the more fundamental principles upon which the interpretation of electrocardiographic records is based were established, before the string galvanometer was introduced into clinical medicine. The more important advances made since that time have come about in the same way as those which preceded them. Few major electrocardiographic problems have been solved by clinical observations alone. For this there are excellent reasons. Our basic knowledge of action currents was acquired by means of direct leads from the tissues under investigation. Unfortunately, it was not possible to study the action currents of the human heart by this method, and indirect leads were necessarily employed for this purpose. The standard limb leads now in universal use have become indispensable, and they are entirely adequate for most of the purposes which clinical electrocardiograms can be expected to serve. They are not, however, capable of furnishing detailed information of the sort obtained when the surface of the exposed heart is explored by means of direct leads. Experiments on animals in which such leads have been employed have consequently continued to play a very important role in the solution of our most difficult electrocardiographic problems. We have not, however, been able hitherto to use all the knowledge acquired in this way to the best possible advantage, because the difference in character between the limb leads used in man and the direct leads used in animal experiments has made it difficult to correlate our clinical and experimental observations. Precordial leads of the type now widely used are much more closely related to direct leads than to the standard limb leads. It is precisely for this reason that they are of such great value. They not only detect lesions which are beyond the range of the standard limb leads, but furnish data that can be directly compared with the data obtained by the use of epicardial leads in animals.

Unipolar Direct Leads.—For the study of cardiac action currents, all kinds of direct leads are not equally satisfactory. In their extensive and detailed study of the course of the excitatory process over the ventricular muscle, Lewis and Rothschild[1] found that it was difficult or impossible to interpret the records obtained when both electrodes were in contact with the ventricular surface. When leads of this kind were used, the cardiac impulse spreading through the ventricular wall from within outward often reached both electrodes at approximately the same time. The deflections recorded under these circumstances were of complicated and variable form and gave no reliable clue to the time of arrival of the impulse beneath either electrode. When, on the other hand, a small electrode in contact with the epicardium was paired with an electrode on the chest wall, the QRS complex almost invariably

displayed a large and very abrupt deflection which was easily recognized and was found to coincide with the activation of the muscle in contact with the exploring electrode. The name "intrinsic deflection" was therefore assigned to it. The other deflections of the QRS group, which were attributed to the excitation of muscle more distant from this electrode, were referred to as "extrinsic deflections," but their origin was not studied in detail.

Because of the character of the laws which govern the distribution of electric currents in three-dimensional conductors such as the body,[2] the magnitude of the potential variations produced by the heartbeat at any point outside the heart itself rapidly diminishes as the distance from the epicardial surface increases. In the course of a cardiac cycle, the variations in potential at a point on the ventricular surface are in the neighborhood of thirty times as large as those displayed by the arms and legs. The deflections of leads from the ventricular surface to some distant part of the body, such as those employed by Lewis and Rothschild, represent the potential variations of the electrode in contact with the heart; the potential variations of the distant electrode are negligible by comparison. It is convenient to use the term "unipolar" to designate leads of this kind in which one electrode is almost completely indifferent, and the term "bipolar" to designate leads like the standard limb leads in which the two electrodes are approximately equidistant from the heart and may, in general, be expected to undergo potential variations of about the same magnitude.

The electrocardiograms reproduced in Fig. 1 were obtained by means of unipolar direct leads from the exposed heart of a dog. Six points on the anterior surface of the ventricle, easy to identify later by their relations to the vessels or other surface markings, were selected, and, from these, control curves were taken with a small exploring electrode. Points *7*, *6*, and *8* were on the right ventricle; the first was on the thickest part of the wall near the atrioventricular groove, and the other two were in the central region close to the trabeculated area which overlies the attachment of the anterior papillary muscle. Points *3*, *1*, and *2* were on the left ventricle; the first was very close to the junction of the free wall and septum, the second near the left margin of the heart, and the third very near the apex. After the control records had been taken, temporary right bundle branch block was produced by pressing upon the right side of the septum above the anterior papillary muscle with the back of a small knife thrust through the wall of the conus arteriosus just below the pulmonary valve. A second set of curves was taken immediately after the knife was withdrawn, and a third set when the right bundle branch had recovered almost completely. Left branch block was then produced by making a cut on the septum just beneath the aortic valve, and a fourth set of records was made. Standard Lead I was taken simultaneously with each direct lead. The intrinsic deflection is easily identified in all of the curves except the first and third from

point *7;* it is the sudden downward movement which begins with the peak of R. The beginning of this deflection, and therefore the peak of R, marks the time of activation of the subepicardial muscle in contact with the exploring electrode. Whether the activation of this muscle and the beginning of the intrinsic deflection coincide exactly or only approximately need not concern us here. It will be noted that, in the leads from the right ventricle, the peak of R fell very late in the QRS interval when right branch block was present and at the very beginning of this interval when left branch block was present. In the leads from points *1* and *2* on the left ventricle these relations are reversed; the peak of R fell late in the QRS interval when left branch block was present and early when right branch block was present. No curve was obtained from point *3* while right branch block was present, for the form of the ventricular deflections of Lead I shows that, when the second tracing was taken from this point, the right bundle branch had already recovered its conductivity. In the lead from point *3* taken after left branch block was produced, the peak of R was not later than before. This point was very close to the septum, and, in our experience, the intrinsic deflection in leads from this region has seldom been much delayed either by left or by right branch block.

When the cardiac mechanism is normal, the intrinsic deflection is always earliest in leads from the trabeculated region, as in the present instance (point *8*). It is only a very little later in leads from the central region but considerably later in leads from points near the atrioventricular groove (point *7*) and from points on the conus arteriosus. The earliest intrinsic deflections found on the left ventricle usually occur in leads from the apex (point *2*), the latest, in leads from the lateral part of the free wall toward the base. This region was not studied in the experiment under consideration. The intrinsic deflection is normally considerably later over the surface of the left ventricle as a whole, than over the surface of the right. This difference is attributable to the greater thickness of the left ventricular wall, for in general the latest intrinsic deflections are found where the muscle is thickest.

Origin of the QRS Deflections.—The origin of the more conspicuous and more constant components of the various kinds of ventricular complexes seen in unipolar direct leads is clearly understood. It must be emphasized that, although the excitation of the muscle in contact with the exploring electrode produces a much larger and much more sudden fluctuation in the potential of this electrode than the excitation of any equal mass of muscle at a greater distance from it, every unit of ventricular muscle, without exception, produces action currents which contribute to the form of these complexes. It is obvious that those components of the QRS complex which precede the intrinsic deflection must be attributed to the excitation of muscle which passed into the active state ahead of the subepicardial muscle beneath the exploring electrode,

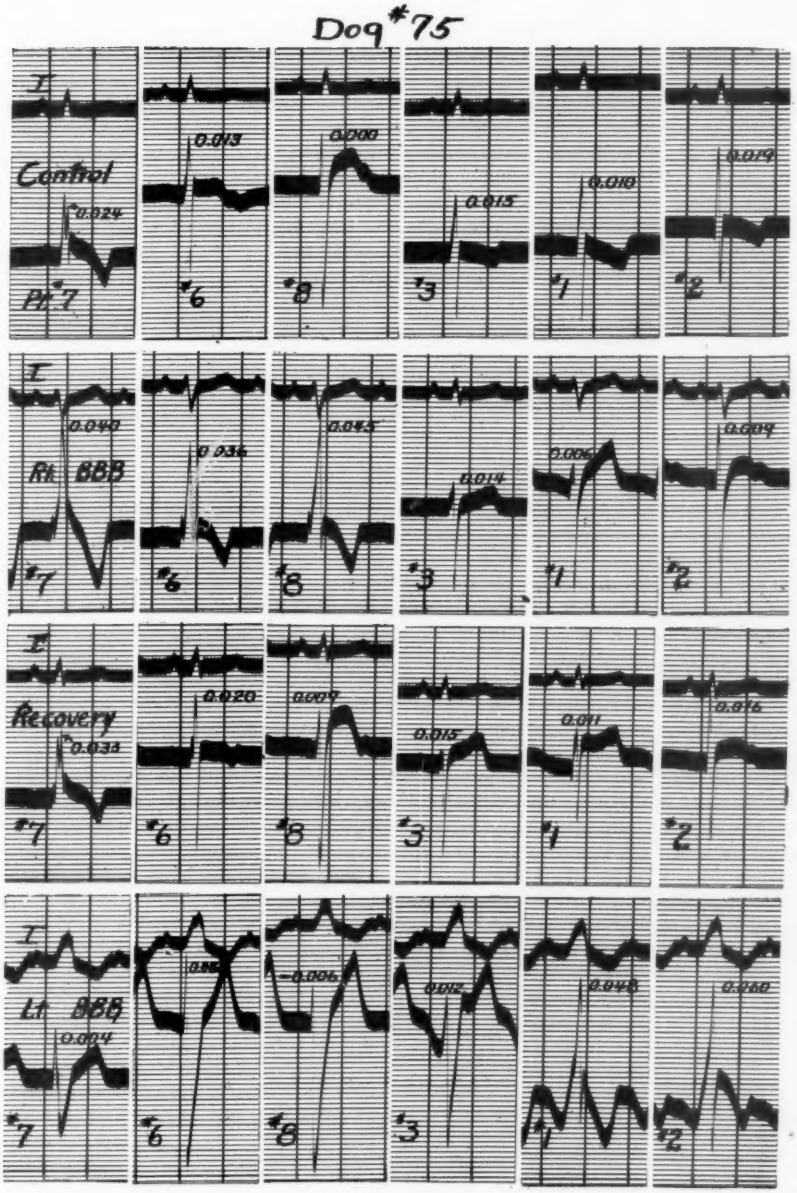

Fig. 1.—Unipolar direct leads from six points on the exposed ventricular surface of a dog's heart.

and that those components which follow the intrinsic deflection must be ascribed to the excitation of muscle that was still in the resting state when the muscle under the contact became active. The peak of R, therefore, separates the QRS components attributable to muscle activated before, from the QRS components attributable to muscle activated after, the cardiac impulse reached the muscle in contact with the exploring electrode.

The resting cardiac muscle fiber is surrounded by a "membrane" which has a very low electrical conductivity. Across this membrane there is an electromotive force which makes its inner surface strongly negative in comparison with its outer surface. The passage of the excitatory process along the fiber is associated with a sudden and very great increase in the conductivity of the resting membrane and a sudden decrease in the electromotive force (Cole and Curtis[3]); in other words, with the sudden development of a short circuit between the inside and the outside of the fiber. Current flows out of the resting part of the fiber adjacent to the short circuit and re-enters the fiber through the short-circuited region. The effect in the medium outside the fiber is the same as if the cardiac impulse were immediately preceded by the positive pole, and accompanied by the negative pole, of a battery. In other words, we may say that, across the boundary between active and resting muscle, there is an electromotive force which makes the potential of points toward which the excitation wave is advancing positive, and the potential of points which lie behind it negative.

The cardiac impulse spreads through the free walls of the ventricles from within outwards and normally enters the septum from both sides simultaneously. Throughout its course it is traveling away from the ventricular cavities, and these are continuously on the negative side of all the boundaries between active and resting muscle. Consequently, the potential of both cavities is negative throughout the QRS interval[4] except in those instances in which one side of the septum becomes active before the other, in which case the ventricular cavity on the side activated last almost always displays initial positivity.

Electromotive forces distant from two neighboring points have approximately the same effect upon the potential of both. It is clear, then, that no cardiac electromotive force except that generated by the muscle between them is capable of producing a large difference of potential between two points which are separated solely by the thickness of the ventricular wall. If the potential of the adjacent part of the ventricular cavity is negative, the potential of an epicardial electrode can be positive only while the excitation wave is passing through the part of the ventricular wall upon which it rests. In taking unipolar leads the galvanometer connections are so made that positivity of the exploring electrode produces an upward deflection in the completed record. The R deflection in unipolar leads from the ventricular epicardium of the

normal heart must, therefore, represent the electrical forces produced by excitation of the muscle between the exploring electrode and the ventricular cavity. The total voltage of these forces is, of course, not measured by the height of the R deflection, but by the difference in potential between the endocardial and the epicardial surfaces of that part of the ventricular wall in contact with the exploring electrode. In bundle branch block most, if not all, of the septal muscle is activated from the contralateral side, and the potential of the homolateral cavity is positive until the cardiac impulse has passed through the septum. Under these circumstances, the R deflection in leads from the outer surface of the delayed ventricle ordinarily displays two peaks. The part of this deflection which precedes the division is due to activation of the septum and represents positivity of the ventricular cavity which is transmitted through the inactive ventricular wall; the part which follows the division is due to activation of the ventricular wall adjacent to the electrode. When this second peak of R is written, the ventricular cavity is negative.

When the excitatory process reaches the muscle in contact with an epicardial electrode, the boundary between resting and active muscle disappears from that part of the ventricular wall upon which the electrode rests. The potential of the electrode then becomes the potential of the adjacent part of the ventricular cavity. The sudden drop in the potential of the electrode when the electromotive force across the wall beneath it disappears is responsible for the intrinsic deflection. The total length of this deflection is an approximate measure of the voltage across the ventricular wall when the cardiac impulse arrived at the epicardial surface.

If the excitatory process is still spreading through some part of the ventricular wall when the intrinsic deflection occurs, the negativity of the ventricular cavity outlasts this deflection and an S wave is inscribed. If, on the other hand, the muscle in contact with the exploring electrode is the last ventricular muscle to pass into the active state, the ventricular cavity is at zero potential when the intrinsic deflection is complete and there can be no S deflection.

If the subendocardial muscle of some part of the ventricular wall passes into the active state earlier than the subendocardial muscle which lies between the exploring electrode and the ventricular cavity, the initial negativity of the cavity is transmitted to this electrode and a Q deflection occurs. If the cavity is initially positive because of circumstances that we have already mentioned, there can be no Q. Since late activation of the subendocardial muscle is likely to be associated with late activation of the subepicardial muscle of the same region, Q deflections are most common in those leads in which the intrinsic deflection occurs late in the QRS interval, and in which, therefore, R is tall and S is small or absent.

In summarizing our remarks on the interpretation of the QRS deflections of unipolar direct leads from the ventricular surface, we may point out that the character of these deflections depends mainly upon the time at which the muscle in contact with the exploring electrode becomes active in relation to the beginning and to the end of the QRS interval. If this muscle becomes active very early in this interval, the R deflection is narrow and usually small and the S wave broad and usually deep. If it is activated very late in this interval, R is tall and broad, S small and narrow, and a Q wave is often present. If it is activated at the very end of the QRS interval, S is absent but there may be a conspicuous Q. As the time of activation of the muscle beneath the exploring electrode approaches the beginning of the QRS interval, R becomes smaller, S larger, and Q less frequent. As it approaches the end of the QRS interval, R becomes larger, S smaller, and Q more frequent. In this discussion we have, of course, not considered many of the perplexing details of the QRS complex which may be encountered in unipolar direct leads as well as in leads of other kinds. Some of these cannot be interpreted satisfactorily until more data are available than at present.

Unipolar Precordial Leads.—The potential of every extracardiac point inside the body is determined by the potential over the heart's outer surface. The potential variations of every element of the epicardial surface contribute in some measure to the potential variations of an electrode placed upon the precordium. But the magnitude of the contribution made by the potential variations of any given surface element is large if its distance from the electrode is small, and vice versa; in fact, it varies roughly as the inverse cube of this distance. For this reason, the potential variations of a precordial electrode are determined to a very large extent by the potential variations of the elements of ventricular surface nearest it. If all or the great majority of these elements simultaneously display potential variations of the same sort, the potential variations of the electrode are of the same character though very much smaller. If, on the other hand, the various elements that are more or less equidistant from the electrode display potential variations of many different kinds, the potential variations of the electrode represent a mixture which may not resemble any of its components very closely.

Since the conditions last mentioned rarely exist, it is almost always possible, by moving an electrode step by step across the precordium, to determine the nature of the potential variations of the various parts of the anterior ventricular surface, provided that the potential variations of the exploring electrode are accurately recorded. In 1929 we began to use multiple precordial leads of this kind to ascertain which of the two ventricles first became active in the classical varieties of bundle branch block. In our first experiments the precordial electrode was paired with an electrode on the left leg. The data obtained in this

way were not entirely conclusive because the components of the QRS complex due to potential variations of the precordial electrode could not be distinguished with certainty from those due to potential variations of the leg electrode.

In man, the potential variations of the precordium are ordinarily three to five times as large as those of the extremities or of the back. When a precordial electrode is paired with an extremity or dorsal electrode, the general outline of the ventricular complex is determined, therefore, to a very large extent by the potential variations of the former and is much the same regardless of whether the latter is placed upon the right arm, the left arm, the left leg, or the left infrascapular region. But in leads of this kind the potential variations of the reference electrode do exert a very considerable influence upon the details of the form of the ventricular complex and make it impossible to utilize the simple principles applicable to the interpretation of the deflections of *unipolar direct leads* in the analysis of the records obtained.

Many seem to believe that precordial leads are merely additional leads comparable in all respects to the standard limb leads. The practice of taking a single precordial lead and calling it Lead IV, a practice which we have never followed, is no doubt partly responsible for this entirely unjustifiable attitude. There is no limit to the number of pairs of points on the trunk which might have served as locations for the electrodes if the "cut and try" method had been used to find the additional leads most likely to prove helpful in those situations in which limb leads had been found inadequate. Precordial leads of the kind under consideration were selected for this purpose because observations dictated by theoretical considerations showed that they are in reality semidirect leads from the anterior ventricular surface, capable within certain limits of serving the same purposes as direct leads from the ventral wall of the exposed heart. They cannot serve these purposes, however, unless the potential variations of the reference electrode are made negligibly small in comparison with those of the exploring electrode. The extent to which the character of the potential variations of the precordial electrode is obscured by the potential variations of the remote electrode determines the degree to which the advantages gained by placing one electrode upon the precordium have been surrendered.

Considerations of this kind led us to devise an artificial ground which reduces the potential variations of the remote electrode to a minimum and makes it possible to obtain essentially unipolar leads from the precordium, from the esophagus, from the extremities, and from other parts of the body. This artificial ground consists of a central terminal which is connected through three equal resistances of 5,000 ohms each to electrodes on the right arm, left arm, and left leg.[5] The effect of this device is to balance out those electric forces responsible for differences in potential between these extremities and consequently for the deflec-

tions of the standard limb leads. It is easily demonstrated that at every instant the potential of the central terminal must be equal to the algebraic mean of the potentials of the three extremity electrodes. On the basis of the assumptions upon which Einthoven's equilateral triangle is founded it has been shown that those components of the heart's resultant electromotive force which are parallel to the plane defined by this triangle have no effect whatever upon the potential of the central terminal. The effects of those components which are perpendicular to this plane cannot be accurately predicted on theoretical grounds. The experiments of Eckey and Fröhlich,[6] Burger,[7] Burger and Wuhrmann,[8] and of others[9] have, however, demonstrated that the largest potential variations of the central terminal do not ordinarily exceed 0.3 millivolt. The potential of this terminal is, therefore, so nearly constant that for practical purposes we may consider it zero throughout the cardiac cycle. We shall then consider all leads unipolar in which an exploring electrode is paired with an artificial ground of this type.

When we began to use precordial leads in our studies of human and experimental bundle branch block, it soon became evident that the most satisfactory way to obtain semidirect leads from both ventricles was to move the exploring electrode across the precordium, along a line roughly perpendicular to the anterior interventricular sulcus and extending from a point at least as far to the right as the right margin of the sternum to a point well beyond the left border of the heart. We have changed our original method of taking precordial leads only as regards the number and the locations of the points explored, which have undergone minor modifications from time to time. We now take unipolar leads from each of the six points specified by the Committee of the American Heart Association for the Standardization of Precordial Leads.[10] In accordance with the recommendations of this committee, these leads are designated V_1, V_2, V_3, V_4, V_5, and V_6. The first of these six points is at the right margin of the sternum in the fourth intercostal space and the second on the left sternal margin at the same level. The remaining points lie on a broken line extending from the second point to the apex beat and thence around the left side of the chest at the apical level. When the apex beat cannot be located, this line is drawn from the second point to the intersection of the left midclavicular line and the fifth intercostal space and is continued around the chest at the level of this intersection. The third point is midway between the second and the left midclavicular line, the fourth in the midclavicular line, the fifth in the anterior axillary line, and the sixth in the midaxillary line. In addition to these six standard leads, we usually take a unipolar lead from the tip of the ensiform cartilage (Lead V_E) and often take unipolar leads from the posterior axillary line (Lead V_7), from the left infrascapular region (V_B), and from other points.

In the precordial electrocardiograms of normal subjects the ventricular complexes of the leads from the right side of the precordium are

strikingly similar to those obtained by placing the exploring electrode directly upon the thinner parts of the anterior wall of the dog's right ventricle (Fig. 2). In these complexes the R deflection is small and narrow and S is deep and relatively broad. The peak of R occurs early in the QRS interval and is followed by a large, abrupt downward movement which obviously corresponds to the intrinsic deflection of direct leads. The ventricular complexes of the leads from the left side of the precordium are similar to those seen in direct leads from the thicker parts of the anterior and left lateral walls of the dog's left ventricle.

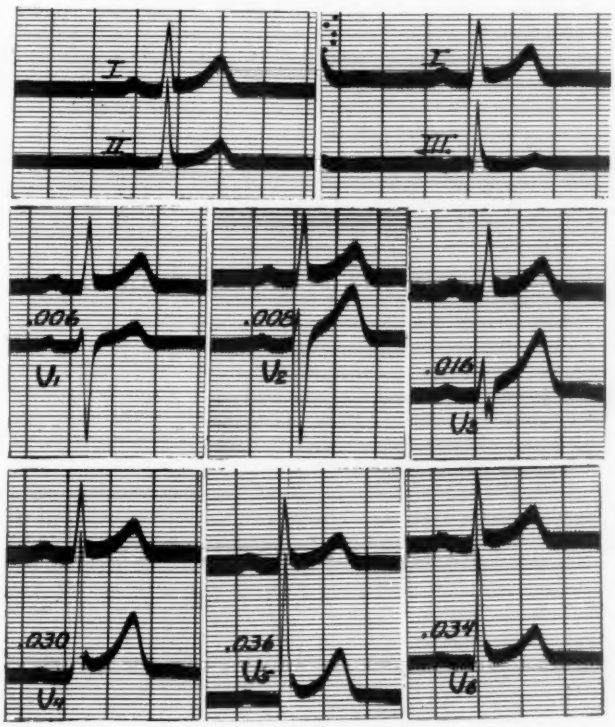

Fig. 2.—The precordial electrocardiogram of a normal subject. The decimals marked on each record give the time of the intrinsic deflection with reference to the beginning of the QRS interval in Lead I, which was taken simultaneously with each precordial lead. (Reproduced from an article by Wilson in Stroud's *Diagnosis and Treatment of Cardiovascular Disease*, by permission of the F. H. Davis Company, Philadelphia.)

The R component of these complexes is tall and relatively wide and it is often preceded by a Q and followed by an S deflection. The peak of R which marks the onset of the intrinsic downstroke is, on the average, about 0.02 second later in leads from the left side of the precordium than in leads from the right side.[11] In precordial leads this downstroke is not nearly so sudden as in direct leads and, therefore, is somewhat more difficult to identify with certainty when the contour of the ventricular complex is complicated or unfamiliar.

TABLE I

THE SIZE OF THE VENTRICULAR DEFLECTIONS IN THE STANDARD AND SPECIAL LEADS (MEASUREMENTS GIVEN IN TENTHS OF A MILLIVOLT)

LEAD	Q				R				S				T				RS			
	MINIMUM	MAXIMUM	MEAN	STANDARD DEVIATION	MINIMUM	MAXIMUM	MEAN	STANDARD DEVIATION	MINIMUM	MAXIMUM	MEAN	STANDARD DEVIATION	MINIMUM	MAXIMUM	MEAN	STANDARD DEVIATION	MINIMUM	MAXIMUM	MEAN	STANDARD DEVIATION
I	0	1.5	0.33	0.45	1.5	19.4	6.81	3.27	0	5.0	1.67	1.35	1.0	5.5	2.21	1.05	3.0	20.6	8.63	3.20
II	0	2.0	0.43	0.61	4.0	22.0	11.99	4.39	0	8.0	1.53	1.92	1.0	6.0	2.97	1.10	8.0	23.0	13.76	3.72
III	0	2.0	0.54	0.60	1.2	18.0	8.50	4.33	0	13.0	1.27	2.40	0	3.0	1.49	0.75	3.2	18.0	10.12	4.10
V_R	0	7.6	2.81	2.68	0	3.0	0.76	0.65	0	10.5	2.56	3.41	-3.3	-0.8	-1.66	0.61	3.5	11.7	6.30	1.82
V_L	0	1.5	0.21	0.42	0	7.0	1.13	1.34	0	7.0	2.00	1.60	-1.0	1.0	0.05	0.41	0.5	8.5	3.27	1.85
V_F	0	1.2	0.29	0.37	0	13.0	6.68	2.81	0	6.5	0.80	1.28	0.2	2.8	1.46	0.62	4.0	13.0	7.66	2.54
V_1	0	0	0	0	1.0	9.6	4.16	2.33	3.4	24.0	11.05	5.03	-4.0	5.6	1.23	1.88	6.6	26.8	15.21	5.98
V_2	0	0	0	0	4.0	20.8	9.05	3.68	3.0	38.8	16.23	7.30	2.4	11.0	6.22	1.90	15.0	46.0	25.27	7.47
V_3	0	0.4	0.013	0.072	6.0	54.6	16.70	9.78	0	22.0	9.05	5.62	3.6	12.0	6.26	1.89	12.6	54.6	25.75	8.37
V_4	0	3.0	0.37	0.68	12.2	46.0	22.31	7.10	0	16.0	5.32	4.13	2.4	11.0	5.66	1.84	18.0	51.6	27.63	6.71
V_5	0	3.4	0.57	0.91	8.8	33.0	18.78	6.91	0	9.6	1.93	2.22	2.0	9.6	4.59	1.82	11.2	33.2	20.70	6.50
V_6	0	0	0	0	2.0	12.8	5.81	2.49	0	16.2	6.09	4.78	0.2	5.2	2.55	1.11	5.6	24.2	11.91	4.33

Between those parts of the precordium which yield small R and deep S waves and those which yield QRS complexes of the opposite kind, there is a zone which yields complexes that are intermediate in form or represent a combination of the deflections obtained at points farther to the right and those obtained at points farther to the left. This zone varies from subject to subject, both in location and in width, and is probably not absolutely constant in either particular in one and the same subject. The ventricular complexes of leads from this transitional zone may display notching and other peculiarities of form. They represent a mixture to which the potential variations of those parts of the right ventricle and the potential variations of those parts of the left ventricle which are least distant from the exploring electrode contribute in approximately equal measure.

The minimal, maximal, and mean voltages of Q, R, S, and T in precordial Leads V_1, V_2, V_3, V_4, V_5, and V_E, and in unipolar extremity Leads V_R, V_L, and V_F, found by Kossmann and Johnston[11] in their study of thirty normal subjects, are given in Table I, which is reproduced in modified form from their paper.

Unipolar Limb Leads.—Unipolar leads from the right arm (V_R), left arm (V_L), and left leg (V_F) furnish a valuable means of comparing the potential variations of these extremities with those of the right and left sides of the precordium and, consequently, of establishing relations between the complexes of the standard limb leads and those of the precordial leads. Unipolar limb leads may be taken by placing the exploring electrode used in taking the precordial leads on each of the extremities in turn or by transferring the wire connected to this electrode to each of the extremity electrodes. When this is done, the deflections obtained are often inconveniently small unless the sensitivity of the electrocardiograph is increased to one and a half or two times its normal value. Goldberger[12] has introduced a procedure which avoids this difficulty. By breaking the connection between the central terminal and the extremity upon which the exploring electrode has been placed, he increases the size of the deflections obtained by fifty per cent without changing the sensitivity of his apparatus. The standard limb leads and the unipolar limb leads are, of course, directly and simply related. The deflections of any two leads of either set furnish all the data needed to compute the deflections of the other four. The equations which express these relations have been published elsewhere[5] and need not be repeated here. It may be pointed out here, however, that when the ventricular complexes of Leads I and II are similar in form, the complexes of Lead V_R resemble the complexes of these leads turned upside down; that when the complexes of Lead III are the inverse of those of Lead I, the complexes of Lead V_L are like those of Lead I; and that when the complexes of Leads II and III are alike, those of Lead V_F have the same form. It should also be remembered that at any instant

the algebraic sum of the potentials of the three extremities is equal to zero.

The Position of the Heart From the Electrocardiographic Standpoint.—The standard and unipolar electrocardiograms of six subjects are reproduced in Fig. 3. Not all of these tracings are normal, but, so far

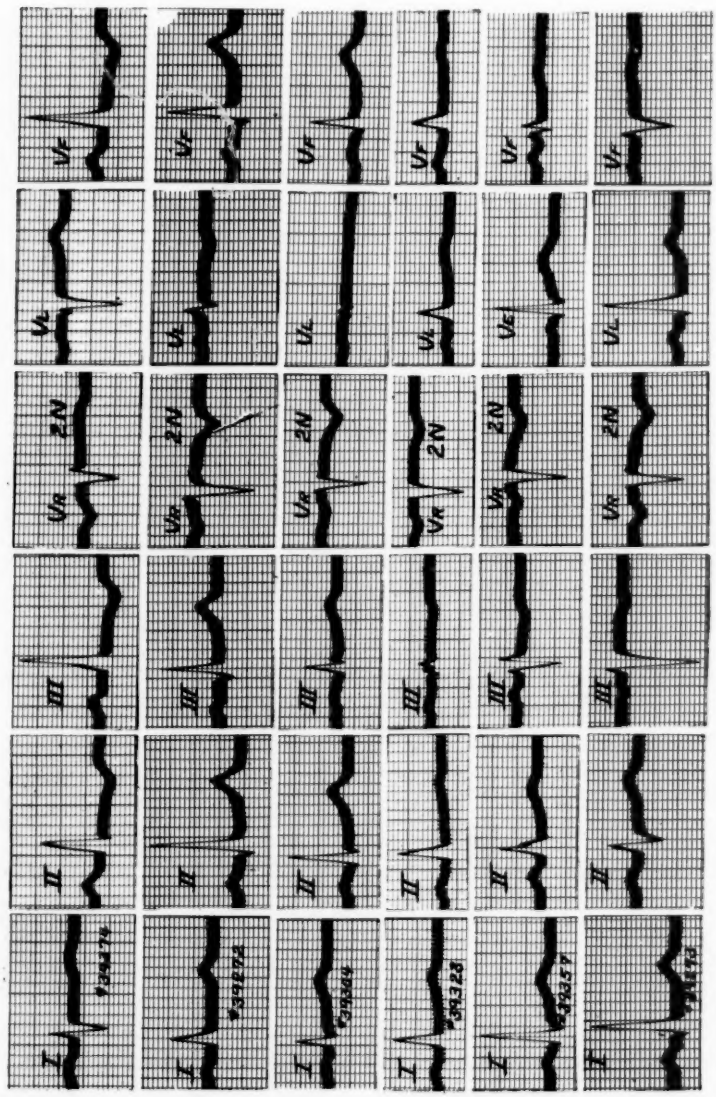

Fig. 3.—The bipolar (Leads I, II, and III) and unipolar (Leads V_R, V_L and V_F) electrocardiograms of six subjects arranged according to the position of the mean electrical axis of QRS. The unipolar limb leads were taken with the galvanometer at twice the normal sensitivity (2*N*). Assuming that the QRS deflections of the precordial leads, had they been taken, would have been of the normal type, the heart was in the vertical position in the first, in the semivertical position in the second and third, in the intermediate position in the fourth, in the semihorizontal position in the fifth, and in the horizontal position in the sixth case. This figure appeared in an article by Wilson, Johnston, Cotrim, and Rosenbaum.[13]

as the QRS complexes are concerned, similar curves could be selected from any collection of normal records. They are arranged in accordance with the position of the mean electrical axis of QRS; the one which displays the greatest degree of right axis deviation is at the top and the one which displays the greatest degree of left axis deviation is

at the bottom. It will be noted that the potential variations of the right arm (V_R) were always of the same general kind. In some cases, this extremity was slightly positive at the beginning, at the end, or both at the beginning and at the end of the QRS interval, but throughout by far the greater part of this interval it was conspicuously negative in all. The potential variations of the other two extremities varied greatly with the position of the electrical axis. When this axis was shifted to the right, as in the first electrocardiogram, the potential variations of the left arm (V_L) were like those which occur over the anterior surface of the dog's right ventricle and over the right side of the precordium in normal subjects. The potential variations of the left leg (V_F), on the other hand, resembled those which occur over the anterolateral surface of the dog's left ventricle and over the left side of the precordium in normal subjects. When the electrical axis was shifted to the left, as in the last electrocardiogram, just the reverse was the case; the potential variations of the left arm resembled those normally found on the left side of the precordium, and the potential variations of the left leg, those normally found on the right side.[13]

When the heart is normal, the precordial electrocardiogram has essentially the same form regardless of whether the limb leads display right axis deviation, no axis deviation, or left axis deviation. It is evident, therefore, that, in normal subjects with right axis deviation, the potential variations of the right ventricular surface are transmitted to the left arm and the potential variations of the left ventricular surface to the left leg, whereas, in normal subjects with left axis deviation, the potential variations of the right ventricular surface are transmitted to the left leg and the potential variations of the left ventricular surface to the left arm. These differences in the magnitudes of the contributions made by the right and left ventricular surfaces to the potential variations of arm and leg can hardly depend upon factors lying within the heart itself; they must be due to variations in the spatial relations between the surfaces of the two ventricles and the attachments of the extremities to the trunk. When the electrocardiogram is normal, there is an obvious correlation between the inclination of the mean electrical axis of QRS and the position of the heart. When the long axis of the heart is nearly vertical, right axis deviation is usually present, and when the long axis of the heart is nearly horizontal, left axis deviation is usually present. We are justified, therefore, in using the terms "vertical" and "horizontal" in defining the position of the heart from the purely electrocardiographic standpoint. So far as the normal heart is concerned, the first five of the six cardiac positions described below could be defined equally well in terms of the position of the electrical axis, but, if that were done, the definitions could not be applied when the heart was abnormal.

From the purely electrocardiographic standpoint, we may then define the following six positions of the heart (Fig. 3).

Vertical Position.—

a. The ventricular complexes of Lead V_L resemble those of Leads V_1 and V_2.

b. The ventricular complexes of Lead V_F resemble those of Leads V_5 and V_6.

Semivertical Positions.—

a. The ventricular complexes of Lead V_F resemble the ventricular complexes of Leads V_5 and V_6.

b. The QRS deflections of Lead V_L are small.

Intermediate Position.—

a. The ventricular complexes of Leads V_L and V_F are similar in form and size and like those of Leads V_5 and V_6.

Semihorizontal Position.—

a. The ventricular complexes of Lead V_L resemble those of Leads V_5 and V_6.

b. The QRS deflections of Lead V_F are small.

Horizontal Position.—

a. The ventricular complexes of Lead V_L resemble those of Leads V_5 and V_6.

b. The ventricular complexes of Lead V_F resemble those of Leads V_1 and V_2.

Indeterminate Position.—There is no obvious relationship between the ventricular complexes of the limb leads and those of the precordial leads.

As long ago as 1910, Kraus and Nicolai[14] asserted that the deflections obtained by leading from the surface of the body are very similar to those that would be obtained by leading from those parts of the heart's surface beneath and nearest the electrodes. They based this opinion upon the principles that govern the distribution of electric currents in volume conductors. As regards precordial leads, we reached a similar conclusion long before we knew that others had held this view, and we have demonstrated that there is a very close relation between the potential variations of a precordial electrode and the potential variations of the underlying ventricular surface. There is considerable evidence of a less direct kind that the potential variations of the right arm are similar to the potential variations of those parts of the heart's surface that are nearest the right shoulder; that the potential variations of the left arm resemble the potential variations of those parts of the heart's surface that are nearest the left shoulder; and that the potential variations of the left leg are like the potential variations of the heart's diaphragmatic surface.

We have already mentioned that the potential of the right arm is ordinarily negative throughout the greater part of the QRS interval. The reason lies in the relation of the right shoulder to the great valvular

orifices at the base of the heart. The negativity of the ventricular cavities is transmitted through these orifices to the adjacent parts of the body, including the right shoulder and the right arm. The potential variations of this extremity do not represent the potential variations of the ventricular cavities in pure form, of course, but mixed with the potential variations of other regions and particularly with those of the surface of the right ventricle. Over the thinner parts of the free wall of this chamber, the potential is normally weakly positive at the very beginning of the QRS interval, but during the rest of this interval it does not differ from that of the ventricular cavity. It is frequently impossible, therefore, to say whether the base of the heart or the right ventricular surface contributed most to the potential variations of the right arm. The same is sometimes true with reference to the potential variations of the left arm. It is well known that when the heart assumes a more vertical position or turns about its long axis in the direction required to bring the left ventricle below the right, the potential variations of the left leg become more like those of the left ventricular surface and less like those of the right ventricular surface, while the potential variations of the left arm change in the opposite way. When the heart assumes a more horizontal position or twists about its long axis in the direction required to bring the right ventricle below the left, the effects upon the potential variations of the left arm and left leg are the reverse of those described.

It is also true that, in myocardial infarction, the potential variations that occur at the epicardial surface of the infarct are transmitted to the left arm when the anterolateral wall of the left ventricle is involved and to the left leg when the diaphragmatic wall is involved.

But although the anatomical position of the heart and its electrocardiographic position are very closely related, there are reasons for believing that the correlation between the two cannot be perfect. It is evident that those parts of the right ventricular surface which play the most important role in determining the potential variations of the right side of the precordium are not identical with those parts of this surface which play the most important role in determining the potential variations of the left arm or left leg, as the case may be. A similar statement may be made with reference to those parts of the left ventricular surface which contribute most to the potential variations of the left side of the precordium. Significant relations between the ventricular complexes of the precordial leads, and the ventricular complexes of the unipolar limb leads of the kind upon which the determination of the electrocardiographic position of the heart is based, can be expected to occur, therefore, only when potential variations of one kind take place simultaneously over a large part of the right ventricular surface and potential variations of another kind take place simultaneously over a large part of the left ventricular surface. This is likely to happen

when the heart is normal, in right and in left bundle branch block, and in preponderant hypertrophy of the right or left ventricle. It is much less likely to happen when there are lesions which give rise to local modifications of the potential variations at the surface of the heart or

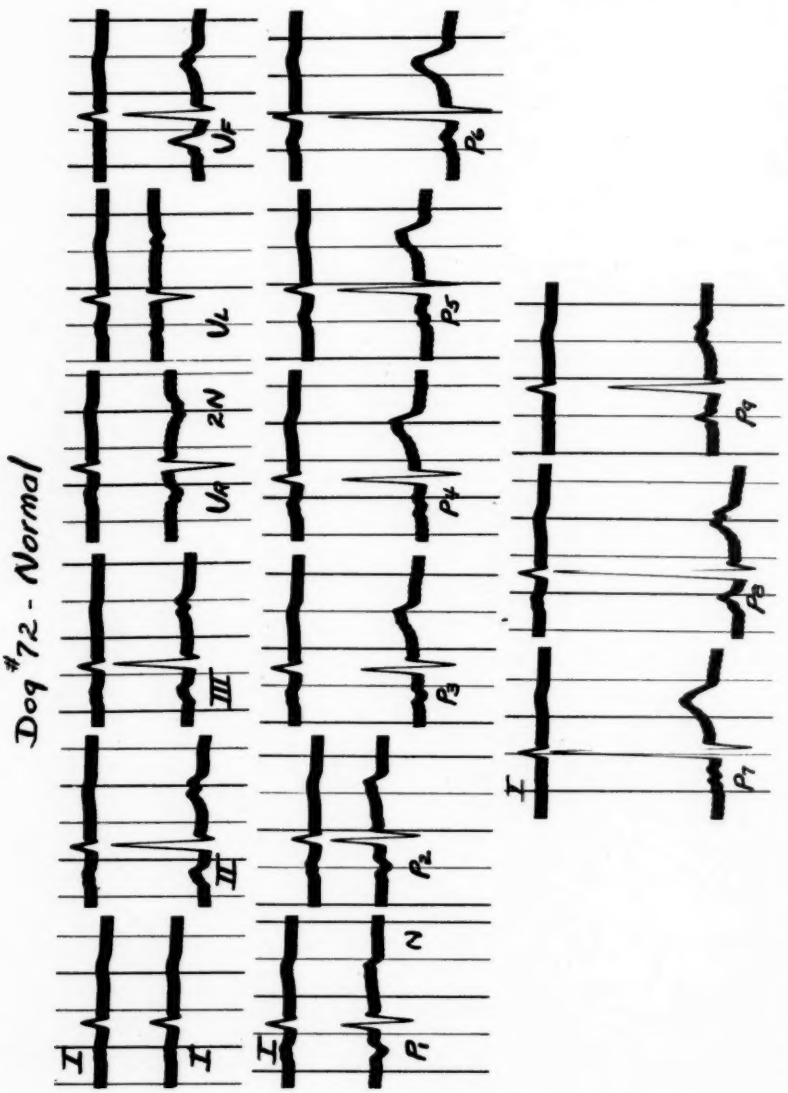

Fig. 4.—The standard electrocardiograms, unipolar electrocardiograms, and precordial electrocardiograms of a normal dog. The potential variations of the left hind leg (V_F) were similar to those of the left side of the precordium (P_7, P_8, and P_9).

which have opposite effects upon the potential variations of different parts of the surface of the same ventricle. For this reason and because the potential variations of the extremities often represent complicated mixtures, it is often impossible in cases of myocardial disease to establish any relation between the potential variations of the precordium and the potential variations of the extremities.

It should be noted that the electrocardiographic position of the heart may change even though the anatomical position remains the same. This is true because the former is determined not only by the orientation of the surfaces of the two ventricles, but also by the distribution of potential variations of various kinds on each of them. In bundle branch block, for example, the regions in which the same kind of potential variations occur at the same time are not exactly the same in extent and configuration as when the heart is normal. Consequently, the onset of bundle branch block may, although it usually does not, alter the position of the heart from the electrocardiographic standpoint.

The Precordial Electrocardiograms of Dog and Man.—The electrocardiograms reproduced in Fig. 4 represent observations made in the course of an experiment upon a normal dog. Standard limb leads, unipolar limb leads, and nine unipolar precordial leads were taken. The first precordial lead was from a point 4 cm., and the second from a point 2 cm., to the right of the midline; the other precordial leads were taken by moving the exploring electrode across the precordium in a base-apex direction and were from points 2 cm. apart. The precordial curves closely resemble the normal human curves obtained by the same method. The potential variations of the two forelegs were similar; both extremities were negative throughout the greater part of the QRS interval (Leads V_R and V_L). The ventricular complexes of Lead V_F are like those obtained from the left side of the precordium (Leads P_5, P_6, P_7, P_8, and P_9) and the deflections of Lead V_L are smaller than those of the other unipolar limb leads. The heart, then, was in the semivertical position.

The electrocardiograms shown in Fig. 5 are reproduced to demonstrate that there are no essential differences between the precordial electrocardiograms obtained in canine bundle branch block and those obtained in human bundle branch block. The curves of the first set represent left branch block in man; those of the second set left branch block in the dog. In both cases the ventricular complexes of the leads from the right side of the precordium display small R and broad S deflections, indicating that the excitatory process arrived at the surface of the right ventricle very early in the QRS interval. The ventricular complexes of the leads from the left side of the precordium, on the other hand, are dominated by broad notched R waves of the kind seen in direct leads from the anterolateral wall of the left ventricle after section of the left branch of the His bundle. The curves of the third set represent human right branch block, and those of the fourth set, canine right branch block. Here the complexes of the leads from the right side of the precordium display a small initial R and a tall final R deflection and are similar to those obtained by leading directly from the surface of the right ventricle after the right branch of the His bundle has been cut. The ventricular complexes of the leads from the left side of the

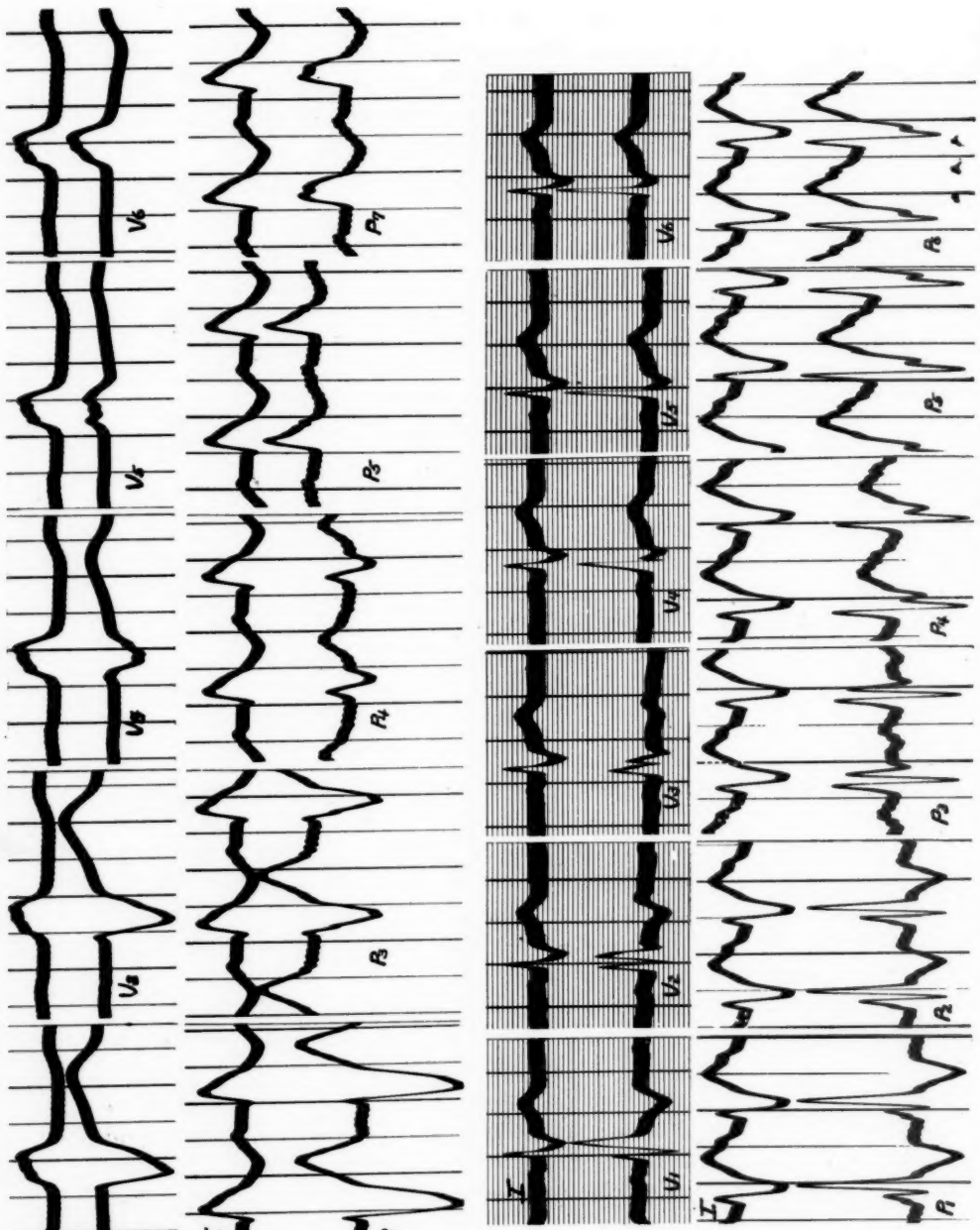

Fig. 5.—The precordial electrocardiogram in bundle branch block. (1) Human left branch block. (2) Canine left branch block. (3) Human right branch block. (4) Canine right branch block.

precordium show narrow R and broad notched S deflections, indicating early activation of the left ventricular surface. It is evident that, if precordial leads instead of limb leads had been used in the early studies of experimental and clinical bundle branch block, human left branch block could never have been mistaken for right branch block over a period of nearly twenty years. The confusion which prevailed over this long period arose because the dog's heart is almost always in the semivertical position, whereas, in patients with arteriosclerotic heart disease, the heart is usually in either the semihorizontal or the horizontal position. Since the relations between the surfaces of the two ventricles and the attachments of the extremities to the trunk are not constant in man, the differentiation of human right, from human left, bundle branch block, on the basis of the data furnished by limb leads alone, is sometimes impossible.

Comparison of Precordial and Direct Leads.—The similarities and differences between unipolar precordial leads and unipolar direct leads from the anterior surface of the heart can be appreciated only when these two kinds of leads are directly compared. In a number of experiments on dogs, we cut one of the branches of the His bundle under aseptic conditions, restored the chest, and allowed the animal to recover completely. Approximately one month after this operation, unipolar precordial leads were taken with the chest intact. The heart was then exposed by splitting the sternum and the potential variations of numerous points on its anterior surface were recorded.

The curves shown in Fig. 6 are from an experiment in which the right branch of the His bundle was cut twenty-six days before the electrocardiographic studies were made. Six of the precordial electrocardiograms are reproduced (P_1, P_3, P_4, P_5, P_6, and P_8). Below these are the records of the potential variations of three points on the right ventricle (points *4*, *5*, and *6*), one point near the interventricular sulcus (point *3*), and two points on the surface of the left ventricle (points *1* and *2*). Point *4* was on the conus, point *5* near the atrioventricular groove, point *6* in the central region, and points *2* and *1* on the left border above the apex.

The first three curves of the bottom row were obtained before the chest was opened by thrusting a sharp exploring electrode, insulated except at the extreme tip, through the chest wall on the right side of the precordium. The first curve was taken when the tip of the electrode was just beneath the skin, the second when it touched the heart and yielded a monophasic response, and the third when it was in the cavity of the right ventricle. The last three curves were obtained in the same way except that the sharp electrode was thrust through the chest wall at a point just inside the apex beat, consequently entering the cavity of the left ventricle. It will be noted that the cavity of this chamber was negative throughout the QRS interval. The potential variations of the

cavity of the right ventricle were not of the usual form inasmuch as the positivity of this chamber, due to the spread of the impulse through the septum from left to right, did not occur at the very beginning of the QRS interval as it ordinarily does. The R wave to which it gave rise is preceded, therefore, by a Q deflection.

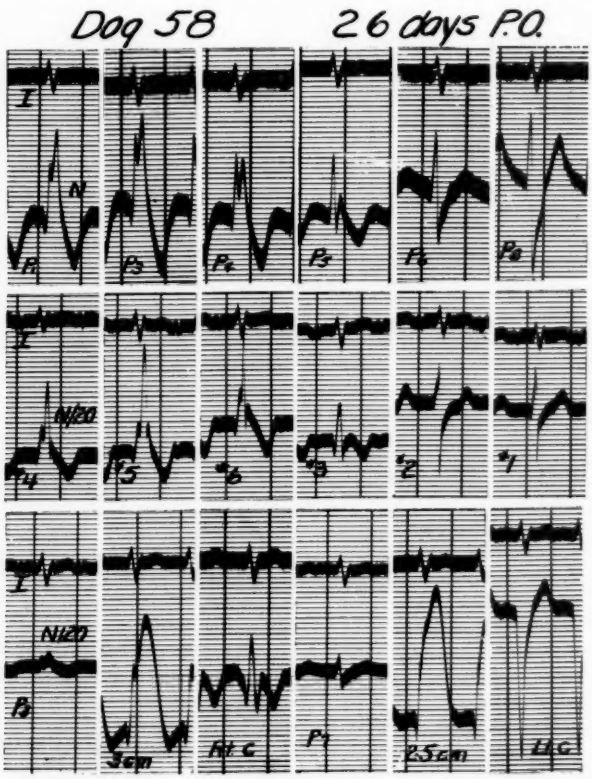

Fig. 6.—Precordial and direct leads in canine right branch block. (1) The precordial electrocardiogram. (2) Direct leads from three points on the right and three points on the left ventricle. (3) *Rt. C*, Potential variations of the cavity of the right ventricle. *Lt. C*, Potential variations of the cavity of the left ventricle.

The curves shown in Fig. 7 are from an experiment in which the left branch of the His bundle was cut twenty-seven days before the electrocardiographic study was made. Eight precordial electrocardiograms are reproduced. Below these are records of the potential variations of the cavity of the right ventricle (*12c*), three points on the right ventricle (*8, 3, 5*), three points on the left ventricle (*6, 1, 7*), and the cavity of the left ventricle (*13c*). Point *8* was near the atrioventricular groove, point *3* in the upper part of the central region, point *5* close to the trabeculated region, point *6* near the apex, and points *1* and *7* on the left border well above the apex. It will be noted that the cavity of the right ventricle was negative throughout the QRS interval while that of the left ventricle displayed initial positivity.

The similarity between the potential variations of the exposed surface of the right ventricle and the potential variations of the right side of the precordium, and between the potential variations of the surface of the left ventricle and those of the left side of the precordium in these two experiments requires no comment. We may point out, however, that the first peak of the bifid R waves often recorded over the delayed ventricle occurs when the cavity of that ventricle is positive, whereas the second peak, which marks the beginning of the intrinsic deflection, occurs when the cavity is negative. In those cases in which the peak of this broad R wave is not divided, the first peak is usually represented by a shoulder on its ascending limb.

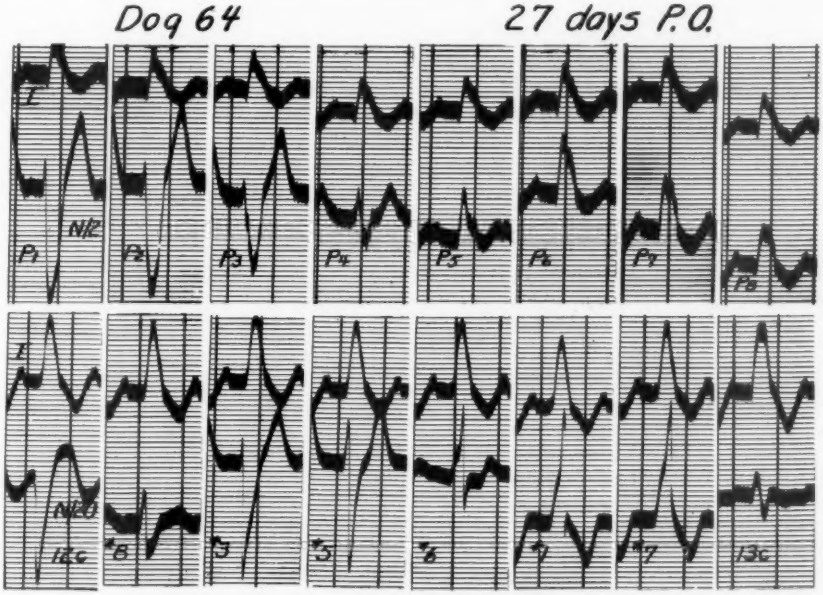

Fig. 7.—Precordial and direct leads in canine left branch block. (1) The precordial electrocardiogram. (2) The potential variations of three points (*8, 3, 5*) on the right, and three points (*6, 1, 7*) on the left ventricle. Potential variations of the cavity of the right (*12c*) and of the cavity of the left (*13c*) ventricle.

Human Bundle Branch Block.—There can be no reasonable doubt that, in man as in the dog, the potential variations of the right side of the precordium (Leads V_1 and V_2) ordinarily resemble the potential variations of the anterior surface of the right ventricle, while the potential variations of the left side of the precordium (Leads V_5 and V_6) ordinarily resemble the potential variations of the anterolateral surface of the left ventricle.

The electrocardiograms shown in Fig. 8 are those of a man who was examined both before and after he developed left bundle branch block. The tracings of March 28, 1940, display slight left axis deviation and flat T waves in Lead II; the QRS interval measures about 0.09 second.

On Dec. 9, 1940, left branch block was present. On this occasion, unipolar limb leads, unipolar precordial leads, and unipolar leads from the left infrascapular region were taken. The potential variations of the left arm (V_L) were similar to those of the left side of the precordium and the left infrascapular region, whereas the potential variations of the left leg were like those of the right side of the precordium in general outline. The heart was then in the horizontal position.

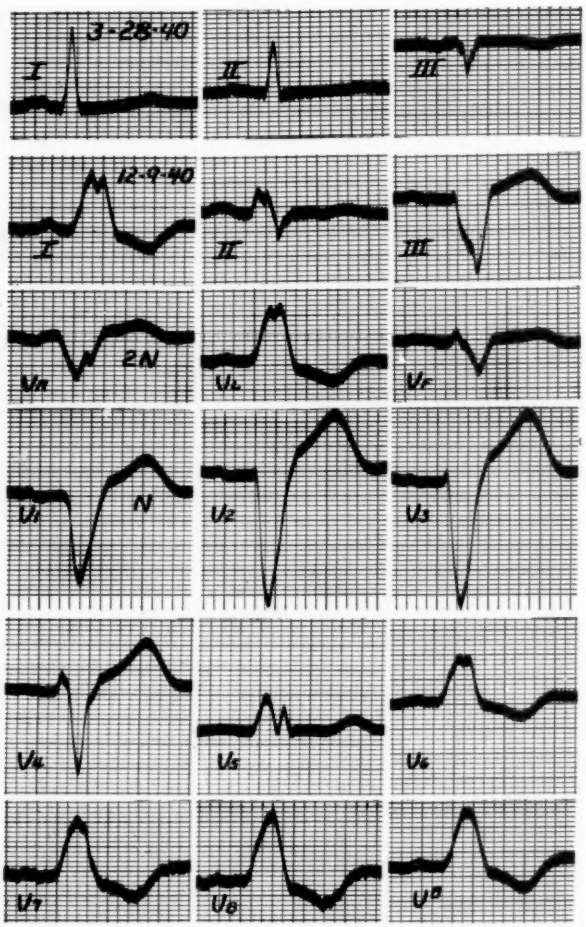

Fig. 8.—Left bundle branch block; heart in the horizontal position.

The electrocardiograms shown in Fig. 9 are those of a tall thin man who was examined for the first time on Feb. 3, 1937, when his electrocardiogram was normal. There was no deviation of the mean electrical axis at this time. On April 14, 1940, left bundle branch block was present and there were broad notched R deflections in Leads I and II and broad S deflections in Lead III. The precordial electrocardiograms of that date differ in no essential particular from those reproduced and

the heart was evidently in the semihorizontal position. On Nov. 27, 1940, and on Dec. 6, 1940, the ventricular complexes of the standard limb leads were of the concordant type. The unipolar leads taken on the latter date show that the potential variations of the left leg were like those of the left side of the precordium and the left infrascapular region. The potential variations of the left arm were small on both occasions. On these two days the heart was in the semivertical position.

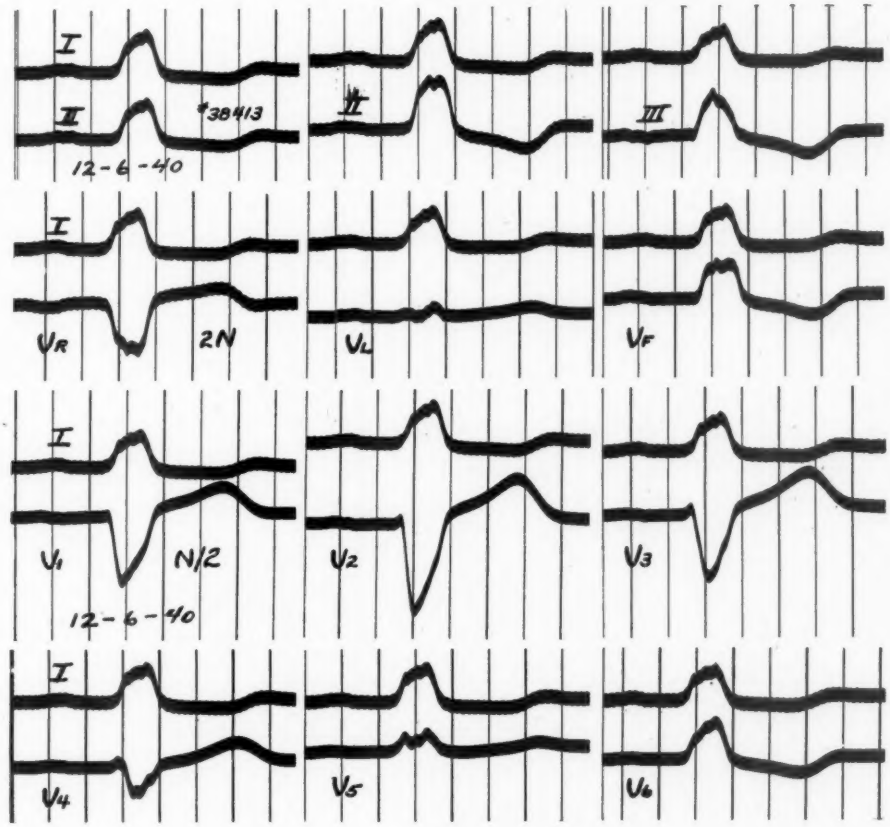

Fig. 9.—Left bundle branch block; heart in the semivertical position.

The patient whose electrocardiograms were reproduced in Fig. 10 was under observation from Feb. 26, 1941, until March 22, 1941. The ventricular complexes of the standard limb leads were quite variable in form. The curves taken on February 28 display discordant ventricular complexes of the kind ascribed to bundle branch block of the rare type. Those taken on March 14 show small bizarre QRS deflections in Lead I and diphasic QRS complexes with broad initial R waves in Leads II and III. In the tracings taken on Feb. 26, March 13, March 18, and March 26, the ventricular complexes are intermediate in form between the two types reproduced. Precordial electrocardiograms were taken on March

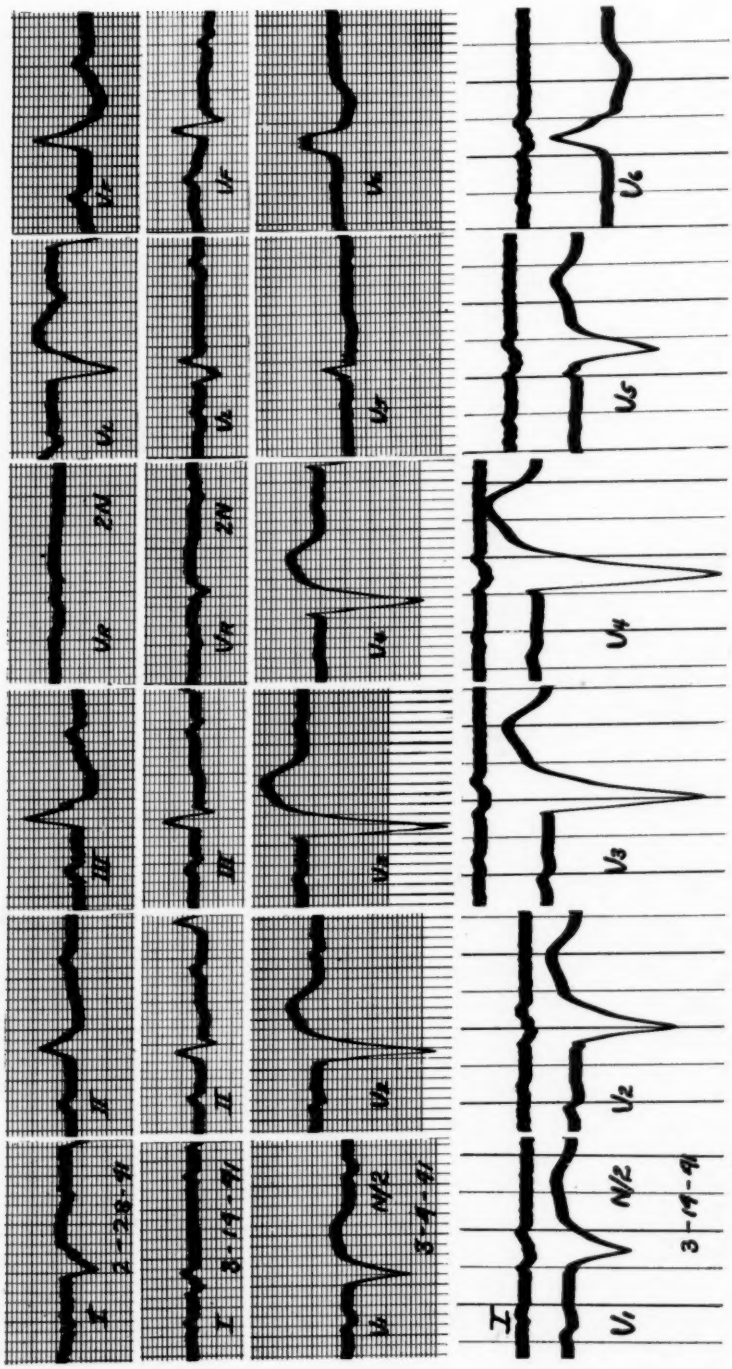

Fig. 10.—Left bundle branch block; heart in the vertical position. (From an article by Wilson.[25])

4 and on March 14, and the two sets of curves differ only as regards the form of the ventricular complexes of Lead V_5. Differences of this kind have no important significance. They are apparently due to variations in the position of the heart or to slight variations in the locations of the precordial points explored. The precordial electrocardiograms demonstrate beyond question that the conduction defect was in the left branch of the His bundle and not in the right.[15] When they are compared with the unipolar extremity curves taken on February 28, it is clear that the heart was then in the vertical position. On that date, the potential variations of the left arm were like those subsequently found on the right side of the precordium and the potential variations of the left leg like those found on the left side of the precordium. On March 14, the heart was in a somewhat different position. On that day, the potential variations of the left arm and of the left leg were apparently complicated mixtures of components transmitted from the surface of the right ventricle, and components derived from the surface of the left ventricle.

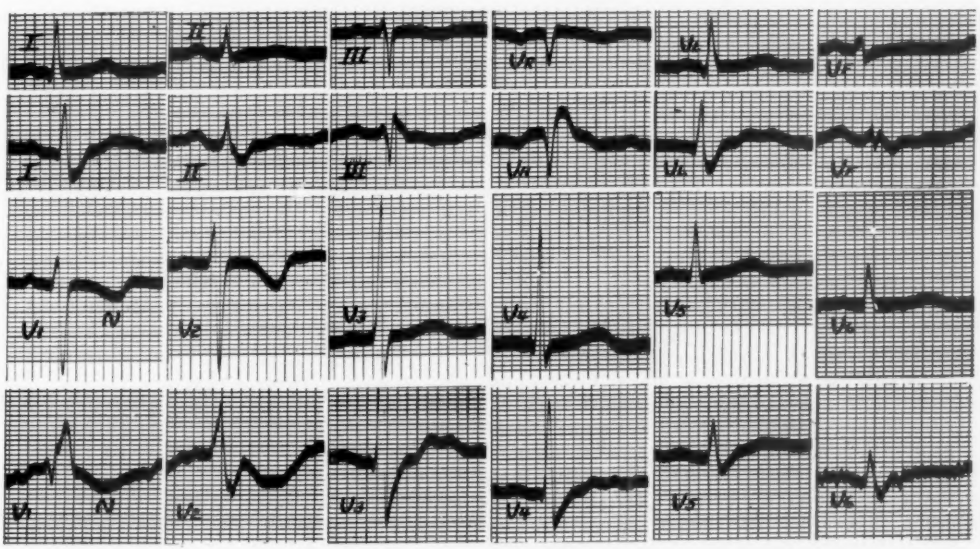

Fig. 11.—Right bundle branch block induced by quinidine; heart in the semihorizontal position.

The electrocardiograms reproduced in Fig. 11 are those of a young woman with ulcerative colitis who developed right bundle branch block on two different occasions after the administration of 0.4 Gm. of quinidine sulfate. Before the drug was given, slight left axis deviation was present, but, apart from inversion of the T waves in Lead V_2, both the standard and the precordial electrocardiogram were within normal limits. In both sets of curves, the ventricular complexes of Lead V_L resemble those of Leads V_5 and V_6, and the deflections of Lead V_F are

small. The heart was then in the semihorizontal position. It will be noted that the onset of right branch block produced more striking changes in the form of the ventricular complexes of Lead V_1 than in the form of those of Leads V_5 and V_6. In the latter, the R wave was slightly smaller and the S deflection deeper and broader after the block than before; in the former, the deep S originally present was replaced by a broad slurred R′ when the block developed. When the cardiac mechanism was normal, the transitional zone which yields complexes intermediate in form between those obtained from points farther to the left and those obtained from points farther to the right lay between precordial points *2* and *3*. When right branch block was present, it lay between points *1* and *2*; only the first precordial lead yielded ventricular complexes of the kind seen in direct leads from the surface of the right ventricle. On the second occasion on which right branch block was induced by quinidine, this apparent shift in the transitional zone did not occur.

The electrocardiograms reproduced in Fig. 12 represent right bundle branch block in a man whose heart was in the semivertical position. The precordial electrocardiogram displays the features usually associated with this conduction defect; the transitional zone lay between points *3* and *4*. In the standard limb leads the ventricular complexes are of the concordant type. The potential variations of the left leg were like those of the left side of the precordium and the potential variations of the left arm were very small.

The electrocardiograms reproduced in Fig. 13 are those of a man, aged 62 years, with arteriosclerotic heart disease. The ventricular complexes of the standard limb leads suggest that left branch block was present. It should be noted, however, that a Q and an S deflection are present in Lead I; both of these components are extremely rare in this lead in left branch block but common in right. The precordial electrocardiogram shows that the conduction defect was on the right side, but it is peculiar as regards the size of the R deflection in Leads V_5 and V_6. The small size of the R waves in these leads suggests that the block was complicated by some factor which diminished the magnitude of the forces produced by activation of the anterolateral wall of the left ventricle. Although no unipolar limb leads were taken, the form of the complexes of the standard limb leads shows that the potential variations of the left leg were like those of the left side of the precordium and the potential variations of the left arm like those of the right side of the precordium. The heart was, therefore, in the vertical position.

When the QRS interval measures 0.12 second or more, and the QRS complex in Lead I is monophasic and consists of a broad, slurred, flat-topped, or bifid R deflection, the precordial curves are, almost always, characteristic of left branch block. When the QRS interval measures 0.12 second or more, and the QRS complex in Lead I is biphasic or triphasic and ends with a broad, slurred or notched S deflection, the

precordial curves are, in the vast majority of cases, characteristic of right bundle branch block. The occasional exceptions to these general rules are due to a number of different causes. When the heart is in the vertical position, the limb leads may suggest that right branch block is

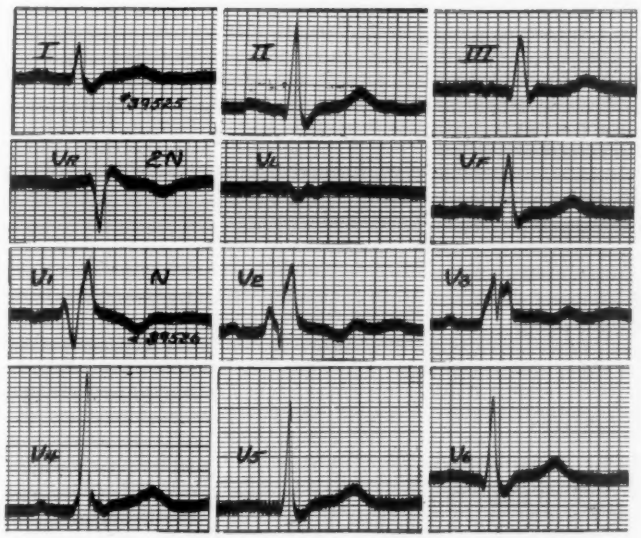

Fig. 12.—Right bundle branch block; heart in the semivertical position.

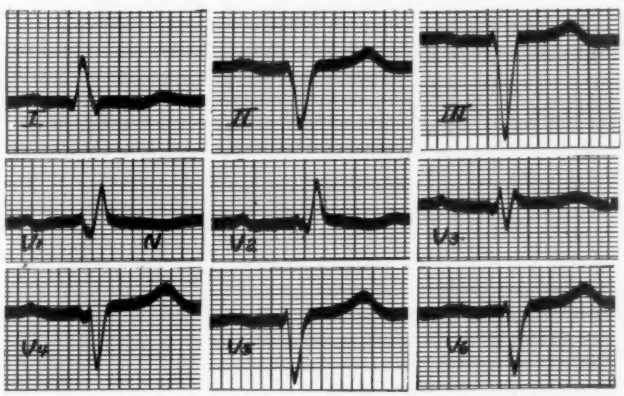

Fig. 13.—Right bundle branch block; heart in the vertical position. (From an article by Wilson.[15])

present when the precordial curves are characteristic of left branch block, and vice versa. In other instances, the prolongation of the QRS interval is due to a general depression of the conductivity of the Purkinje tissue or to local lesions involving the subendocardial Purkinje network over a considerable area ("arborization block").[16] The latter is seen most often in association with extensive myocardial infarction.

When the QRS interval measures 0.12 second or more, and the precordial electrocardiogram shows some but not all of the features typical

of right or of left branch block, the conduction defect cannot be located with certainty. Sometimes this situation arises because this defect is associated with lesions which modify its effects upon the electrocardiogram. Sometimes it depends upon peculiarities in the extent or location of the transitional zone, which separates the parts of the precordium that display potential variations like those of the anterior surface of the right ventricle, from the parts of the precordium that display potential variations like those of the anterolateral surface of the left ventricle. This may be so far to the left or so far to the right that all of the six standard precordial leads yield ventricular complexes of the same type. When this happens, it is desirable to take additional unipolar leads so arranged as to cross this zone. It is still impossible to say why the transitional zone is so variable in width and location. Finally, it should be emphasized that in many cases of bundle branch block there is no obvious relation between the form of the ventricular complexes of the precordial leads and the form of the ventricular complexes of the limb leads. In these cases the position of the heart must be classed as indeterminate.

When the QRS interval is abnormally long but measures distinctly less than 0.12 second, the precordial curves are seldom characteristic of complete bundle branch block. In rare instances they are typical of right branch block even though the QRS interval of the limb leads is not much greater than 0.10. In most of the cases of this kind that we have seen we suspected that the right ventricle was greatly hypertrophied, and it is possible that this condition was in part responsible for the form of the precordial electrocardiogram.

Unipolar precordial leads make it possible to diagnose incomplete right bundle branch block in many cases in which it cannot be recognized by other means. Except under special circumstances, the diagnosis of incomplete left branch block is still very difficult to make with certainty.

The electrocardiograms reproduced in Figs. 14 and 15 represent the alternation of complete with incomplete right branch block. The first ventricular complex of each pair represents complete, and the second incomplete, block. It will be noted that as regards their earliest components the paired complexes are identical in all leads. In the case of the limb leads and the leads from the left side of the precordium (V_5 and V_6), the sole difference lies in the width of the final QRS component and the size of the T deflection. In the leads from the right side of the precordium (V_1 and V_2), from the tip of the ensiform process (V_E), and from the right nipple line, the difference is much greater; the large final R′ deflection of the first complex is very much smaller (V_1 and V_E) or embryonic* in the second (V_2). The presence of such

*This term is used to indicate that the peak of this deflection does not rise above the level of the trace at the beginning of the QRS interval.

small or embryonic R′ deflections, in addition to an initial R wave in the leads from the right side of the precordium, strongly suggests that incomplete right branch block is present, particularly when the QRS interval is slightly increased and there is a broad S wave in Lead I and in the leads from the left side of the precordium. It is advisable to take precordial leads whenever the QRS complex of Lead I is of this kind.

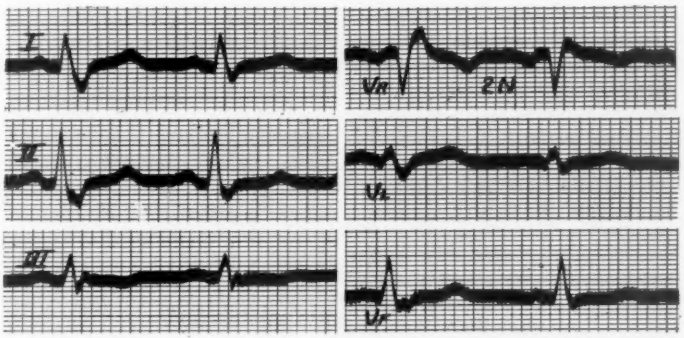

Fig. 14.—Complete and incomplete right bundle branch block; standard and unipolar limb leads.

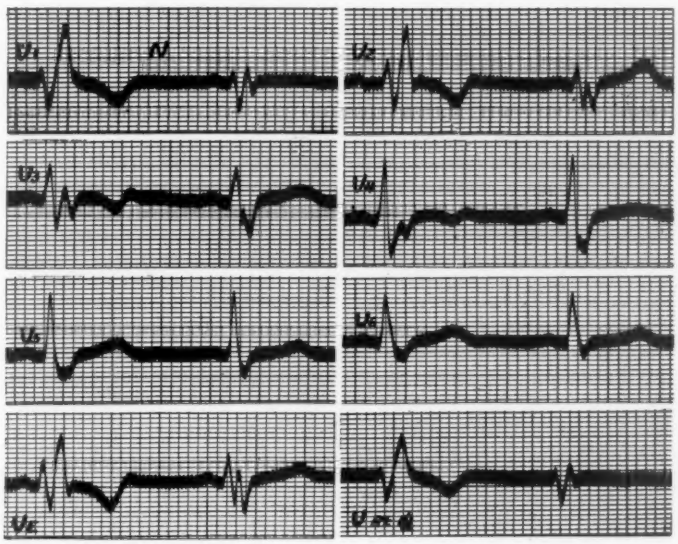

Fig. 15.—Complete and incomplete right branch block; precordial leads.

In incomplete left bundle branch block, the precordial electrocardiogram resembles that seen in preponderant hypertrophy of the left ventricle and the two conditions frequently coexist. The presence of a Q deflection in the leads from the left side of the precordium excludes the former, but the absence of this deflection does not differentiate one from the other.

Transient Branch Block.—In the vast majority of the cases of human bundle branch block, there is no way of knowing whether all the electrocardiographic abnormalities present are due to the conduction defect or whether some of them are the result of the other lesions which are almost always present. Cases in which the electrocardiogram is normal after branch block disappears, or immediately before it develops, are, therefore, of unusual interest. In such cases the effects produced by the block are uncomplicated by other factors.

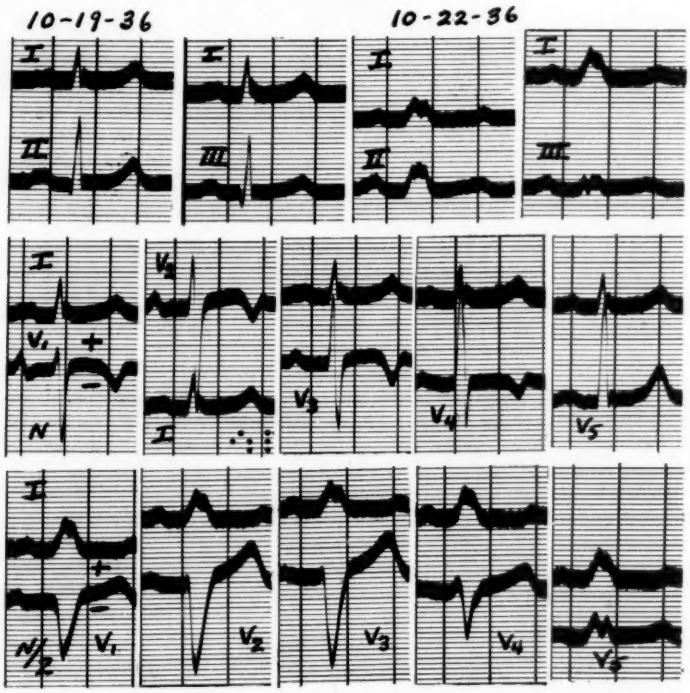

Fig. 16.—Transient left branch block.

The electrocardiograms reproduced in Fig. 16 are those of a woman, aged 55 years, who had symptoms suggesting hyperthyroidism. She was under observation from Oct. 13, 1936, until Nov. 3, 1936. Left branch block was present when the patient was seen for the first time, but, on October 19, the standard extremity curves were normal. At this time the precordial curves were normal as regards the QRS complexes, but the T waves were sharply inverted in Leads V_1, V_2, V_3, and V_4. This case conforms to the rule that abnormalities which are confined to the leads from the right side of the precordium are not accompanied by similar abnormalities in the limb leads. It illustrates the value of precordial leads in detecting lesions which produce electrocardiographic disturbances of this kind. On October 22, the branch block was again present. In the standard leads the broad notched QRS deflections were of

low voltage and of the concordant type. In the precordial leads the voltage of the chief QRS deflection was so large that, in order to record it properly, it was necessary to reduce the string galvanometer to one-half the normal sensitivity. It will be noted that the conduction defect greatly reduced the size of the R waves in the leads from the right side of the precordium, abolished the inversion of the T waves previously present in these leads, and shifted the transitional zone to the left. In the leads from the left side of the precordium (V_5 and V_6), it gave rise to monophasic QRS complexes consisting of broad, bifid R deflections. It is evident that the heart was in the semivertical position.

The electrocardiograms reproduced in Fig. 17 are those of a woman, aged 24 years, with rheumatic heart disease. She was under observation from Nov. 16, 1938, until April 25, 1939. When she was first seen, the electrocardiogram displayed rather large P deflections, but was not definitely outside normal limits. On April 5, the P-R interval measured 0.32 second, and right branch block was present. On April 14, the electrocardiogram was normal and precordial leads were taken. On April 25, right branch block was again present and the precordial leads were repeated. It will be noted that the block gave rise to a large final R′ deflection in Leads V_1 and V_2, inverted or flattened the T waves in the first four precordial leads, made the R deflections somewhat smaller in the leads from the left side of the precordium, and produced broad S waves in Leads V_5 and V_6.

Ventricular Hypertrophy.—Preponderant hypertrophy of the left ventricle increases the thickness and the bulk of its walls. When uncomplicated, its chief effect is, therefore, to exaggerate the normal difference in this respect between this chamber and its fellow. It is not surprising, then, that in left ventricular hypertrophy, unipolar precordial leads yield curves which, in their broader aspects, are not unlike those obtained when the heart is normal. The chief differences are these: In left ventricular hypertrophy the voltage of the chief deflection of the QRS group is on the average much greater than normal, and the QRS interval is increased to 0.10 or even 0.11 second. In the leads from the right side of the precordium the R deflections are, on the average, much smaller than normal and may be absent.[17] The transitional zone is, as a rule, much displaced to the left. In the leads from the left side of the precordium, R, and often Q as well, is abnormally large; the peak of R occurs abnormally late in the QRS interval; and the T deflections are inverted.

By increasing the bulk and thickness of its walls, preponderant hypertrophy of the right ventricle tends to abolish or reverse the normal difference between it and the left. In high-grade right ventricular hypertrophy, the precordial curves are, as regards their broader aspects, somewhat like those obtained in right branch block, but the QRS inter-

val is not increased and the QRS deflections are not ordinarily broad, slurred, or notched. On the average, the voltage of the chief QRS deflection is above normal although not as large as in left ventricular hypertrophy.[17] In the leads from the right side of the precordium,

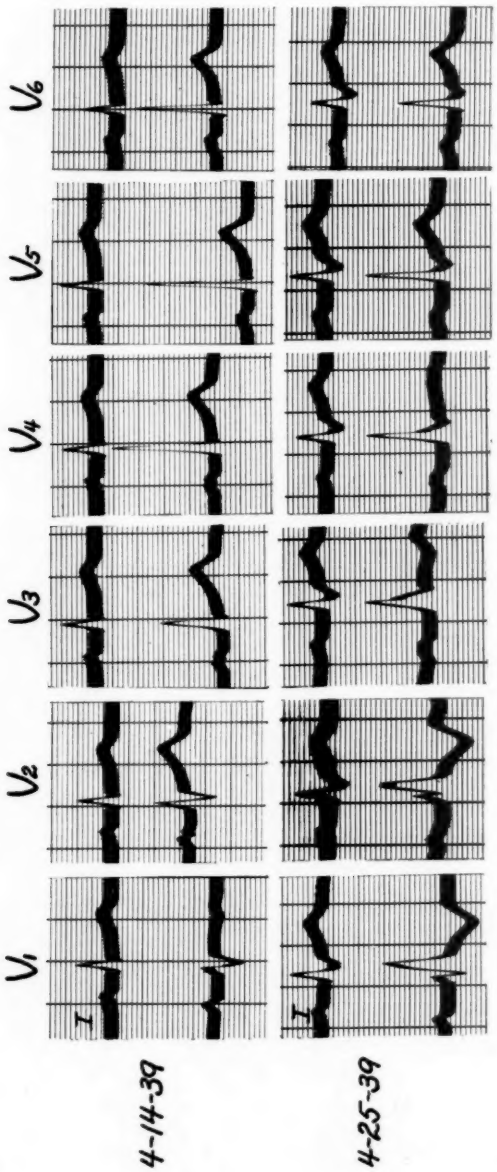

Fig. 17.—Transient right branch block.

the R wave is very large, Q is frequently present, S is usually absent, and the T deflections are commonly inverted. In some instances a small initial upward deflection precedes the first downward deflection of the

QRS group, but we suspect that the presence of such a summit may be due to incomplete right branch block. In the leads from the left side of the precordium the R deflections are abnormally small and the S deflections abnormally large. In other words, the precordial curves are opposite in type to those obtained when the heart is normal.

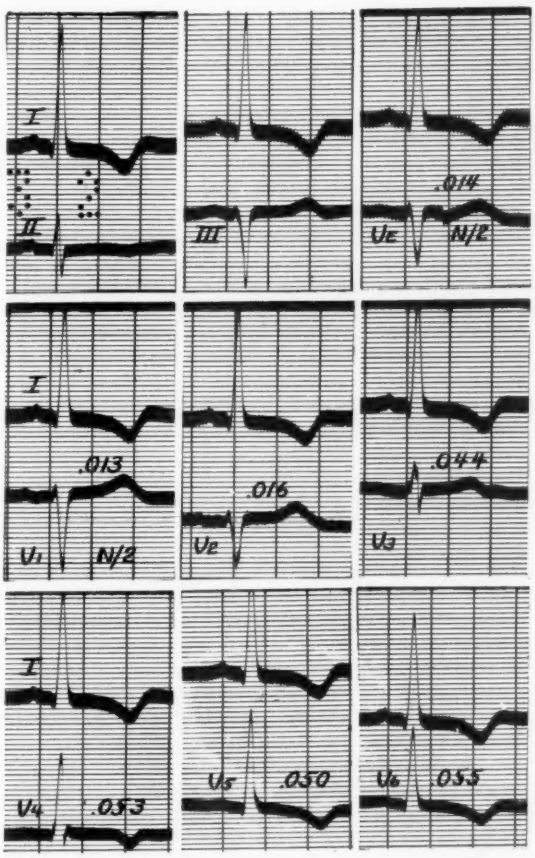

Fig. 18.—Left ventricular hypertrophy; heart in the horizontal or semihorizontal position.

In left ventricular hypertrophy the position of the heart has the same effect upon the mean electrical axis of QRS as in normal subjects. The electrocardiograms reproduced in Fig. 18 are those of a man, aged 54 years, with hypertensive heart disease. The standard extremity curves display left axis deviation, a QRS interval measuring approximately 0.10 second, and prominent Q waves, abnormally large R deflections, and inverted T waves in Lead I. The precordial curves, which were taken with the galvanometer at one-half the normal sensitivity, are characteristic of left ventricular hypertrophy. Although no unipolar limb leads were taken, it is clear that the heart was in the horizontal or semihorizontal position.

The electrocardiograms reproduced in Fig. 19 are those of a woman, aged 50 years, with hypertensive heart disease. No axis deviation is present, but the R deflections are abnormally tall and the T waves inverted in all of the standard limb leads. The QRS interval is slightly increased. The precordial curves, which were taken with the galvanometer at one-half the normal sensitivity, are characteristic of left ventricular hypertrophy. The potential variations of the left leg were like those of the left side of the precordium and the potential variations of the left arm were small. The heart was in the semivertical position.

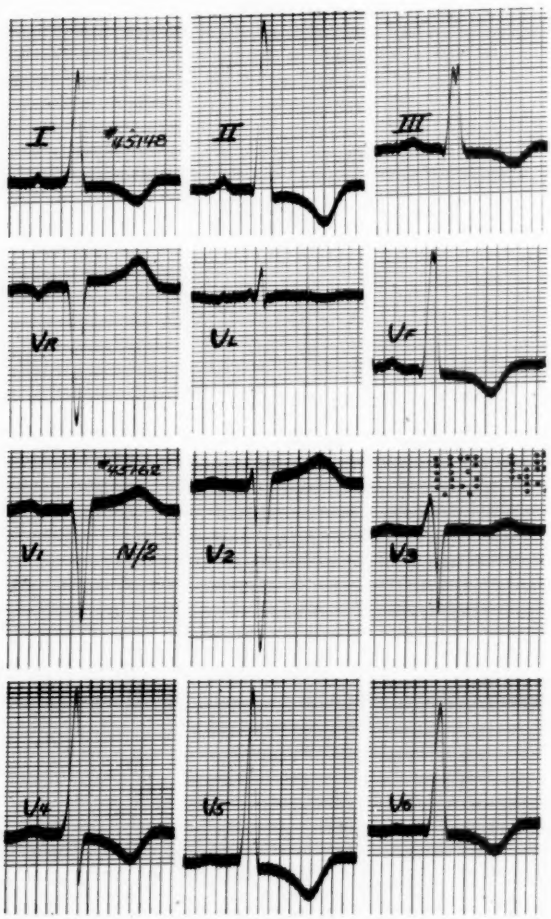

Fig. 19.—Left ventricular hypertrophy; heart in the semivertical position.

The electrocardiograms reproduced in Fig. 20 are those of a young man, aged 16 years, with rheumatic heart disease, aortic stenosis and regurgitation and probably mitral stenosis, and an enormously enlarged heart. Right axis deviation is present, the T deflections are inverted in Leads II and III, the P-R interval is increased, and the P deflections

are large and deformed. Seven precordial leads were taken, the last, marked V_7, from the posterior axillary line at the level of the apex, which was not far inside this point. The precordial curves, which were taken with the galvanometer at one-half the normal sensitivity, are characteristic of left ventricular hypertrophy. Although unipolar limb leads were not taken, it is evident the potential variations of the left leg were like those of the left side of the precordium and the potential variations of the left arm like those on the right side of the precordium. The heart was, therefore, in the vertical position.

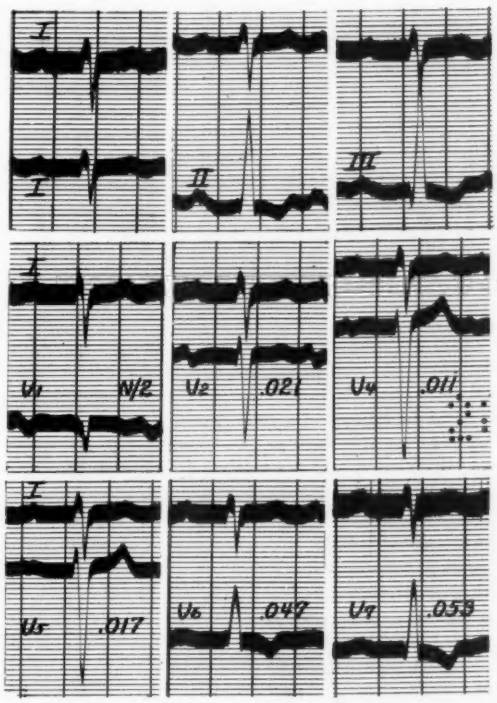

Fig. 20.—Left ventricular hypertrophy; heart in the vertical position. (From an article by Wilson, Johnston, Cotrim, and Rosenbaum.[13])

The electrocardiograms of two patients with right ventricular hypertrophy are reproduced in Fig. 21. The curves of the upper set are those of a woman, aged 34 years, who had pulmonary hypertension of unknown origin. The limb leads display conspicuous right axis deviation. The precordial curves are characteristic of right ventricular hypertrophy; tall R waves, prominent Q waves, and inverted T waves are present in Lead V_1, and small R and deep S waves in Leads V_5 and V_6. The potential variations of the left arm were like the potential variations of the left side of the precordium, and the potential variations of the left leg resembled those of the right side. The heart was in the horizontal position. The curves of the second set are those of a

man, aged 40 years, with mitral stenosis and aortic insufficiency. The precordial curves are characteristic of right ventricular hypertrophy. Large S waves and small R waves are present in all of the standard

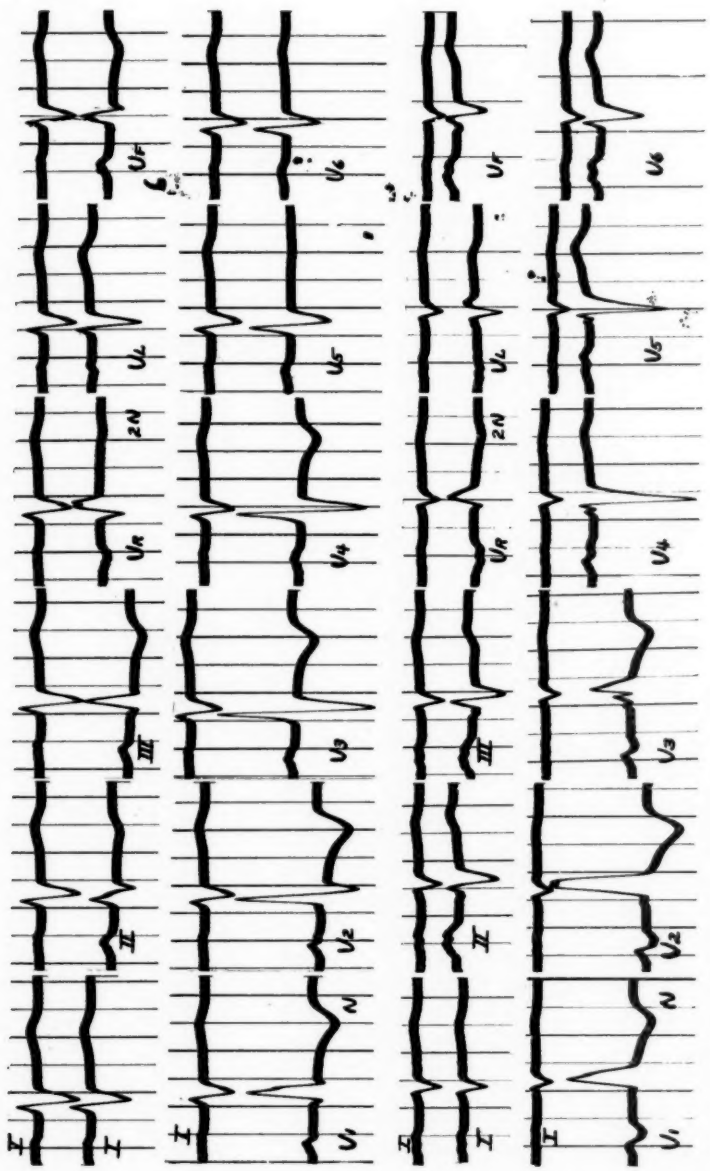

Fig. 21.—Right ventricular hypertrophy. (1) Heart in the horizontal position. (2) Heart in the semivertical position.

limb leads. Here the ventricular complexes of the unipolar leg lead are like those of Leads V_5 and V_6; the complexes of the right arm lead are like those of Lead V_1, and the complexes of the left arm lead apparently represent a mixture of the potential variations of the other two ex-

tremities. In this case the heart was apparently in the semivertical position.

When the heart is greatly enlarged, it is ordinarily in the horizontal or semihorizontal position. In either case, left ventricular hypertrophy produces left, and right ventricular hypertrophy produces right, axis deviation. When the heart is in the semivertical position, left ventricular hypertrophy produces abnormally tall R waves and, usually, inverted T waves, and right ventricular hypertrophy produces large S waves in all of the standard limb leads. When the heart is in the vertical position, left ventricular hypertrophy produces right, and right ventricular hypertrophy should produce left, axis deviation, although we have not as yet seen the latter occur.

The precordial curves of left ventricular hypertrophy are distinguished from those of left bundle branch block by the absence of slurred or bifid R waves and the great frequency of Q deflections in the leads from the left side of the precordium. In left branch block, the presence of Q in these leads suggests that the diagnosis is wrong or that septal lesions which prevent initial positivity of the left ventricular cavity are present. The QRS interval is almost always less than 0.12 second in hypertrophy, whereas, in block, it equals or exceeds this figure.

The precordial curves of right ventricular hypertrophy are distinguished from those of right bundle branch block by the absence of double or bifid R waves in the leads from the right side of the precordium, by the small size of the R waves in the leads from the left side of the precordium, and by the absence of a greatly increased QRS interval.

It must be admitted, however, that cases are frequently encountered in which it is impossible to say with certainty whether the electrocardiographic changes are due to hypertrophy alone or to hypertrophy plus incomplete bundle branch block.

Myocardial Infarction.—The character of the potential variations at the epicardial surface of an infarct depends upon the stage of infarction and upon whether the whole thickness of the ventricular wall or only the subendocardial layers of muscle are involved. Immediately after ligation of the anterior descending coronary artery or one of its branches in experiments upon the dog's heart, direct leads from the region supplied by the vessel occluded display pronounced upward displacement of the RS-T junction, which persists for many hours but disappears when the muscle affected dies or recovers.[18] This RS-T displacement is accompanied by a corresponding reduction in the voltage of the intrinsic deflection. When the whole thickness of the ventricular wall is involved and the infarcted muscle is already dead or incapable of responding to the excitatory impulse, the potential variations of the part of the ventricular cavity adjacent to the infarct are faithfully transmitted to its epicardial surface. Since the ventricular cavities

are normally negative throughout the QRS interval, direct leads from the central part of the infarct then yield QRS complexes which consist of a monophasic downward deflection (QS deflection). In many cases, some fraction of the muscle in this region remains alive and gives rise to an embryonic R wave which produces a notch on the descending or ascending limb of the single QRS component. When the subendocardial layers of muscle are for the most part dead or incapable of responding to the cardiac impulse, and the outer layers of muscle are relatively normal, the embryonic R rises above the base line and becomes a true R deflection. The QRS complex then consists of an abnormally large Q followed by a small R and often by an S deflection also. Since infarcts of the left ventricular wall are usually more extensive on the endocardial than on the epicardial side, QRS complexes of this kind are commonly seen in direct leads from the marginal parts of the infarcted area.[19] These same zones also yield deep, sharply inverted T deflections due to an increase in the duration of the excited state at the epicardial surface. In the dog, the T-wave changes develop some hours after infarction begins, and ordinarily disappear almost completely within twenty-four hours or less. In man, they commonly last for some weeks or months.

The potential variations of the epicardial surface of the infarcted region are transmitted to the adjacent parts of the body. When the anterior wall of the left ventricle is involved, they are transmitted to the precordium; if the anterolateral wall is involved, they are also transmitted to the left arm. If the posterior wall is infarcted, they are usually transmitted to the ventricular levels of the esophagus, to the back, and to the left leg. The potential variations of points at some distance from the heart but on the same side of it as the infarcted region are, of course, a mixture of components derived from the epicardial surface of the infarct, from regions adjacent to it, and from other parts of the ventricular surface. It is only when the infarct is large that characteristic curves are obtained by leading from regions distant from it. The potential variations of parts of the body on the side of the heart opposite the one involved, as regards their general character, are the inverse of those that occur at the surface of the infarct.

The diagnosis of myocardial infarction can be made with certainty from the electrocardiogram alone only when characteristic changes in the QRS complex occur in association with RS-T displacement or typical changes in the T deflections. Changes in the QRS complex have more diagnostic value than displacement or changes in the T waves when only electrocardiographic data are available, but they are not conclusive. When clinical data are available and are strongly suggestive of infarction, and serial curves are taken, the opposite is true because of the relatively rapid, progressive changes which the T complex undergoes. Similar changes may occur in pericarditis, but usually this can be ruled out on clinical grounds.

From the electrocardiographic standpoint, there are many types of infarcts which differ one from another as regards the character of the electrocardiographic changes and the leads in which they occur. Whether some of these varieties are determined by the position of the heart rather than the location and extent of the infarcted region, only the future can decide.

T-Wave Changes Only.—The electrocardiograms reproduced in Fig. 22 are those of a physician, aged 67 years, who was first seen on Aug. 7, 1934. At that time, the standard limb leads showed a considerable shift of the electrical axis to the left, but no other notable features. Myocardial infarction occurred early in March, 1940. Six weeks later (April 25, 1940) there was sharp inversion of the T deflections in all of the precordial curves although the limb leads showed no significant changes. After eight months, all electrocardiographic evidence of infarction had completely disappeared. The patient made an uneventful recovery. We have seen no instance of serious cardiac impairment following anterior infarction which produced no electrocardiographic abnormalities other than sharp inversion of the T waves.

Transient QRS Changes.—The electrocardiograms reproduced in Fig. 23 are those of a man who began to have symptoms typical of coronary thrombosis at 6:40 P.M., on Oct. 6, 1936, while he was under treatment for prostatic hypertrophy. On the following day, the standard electrocardiogram showed extremely small QRS deflections and flat T waves in Lead I. In the precordial leads there was a progressive diminution in the size of R as the exploring electrode was moved from the first to the fourth position, and this deflection was abnormally small in Leads V_5 and V_6. A month later, the QRS deflections were normal, but there was sharp inversion of the T waves in all of the limb leads and in the last four precordial leads. The patient's recovery was complete and uninterrupted.

It is apparent that, in this instance, the infarcted muscle was, for a time, incapable of responding to the excitatory impulse, but it was not dead and subsequently recovered its excitability. Very pronounced alterations in the QRS complex of the kind observed in this case seldom disappear completely, but they often undergo a very slow and much less pronounced retrogression. Very often, clear-cut and characteristic deformities of this complex and, much more rarely, residual changes in the T waves are still present years after the cardiac accident. An instance of this kind is illustrated in Fig. 24. The patient developed myocardial infarction in May, 1934, when he was 23 years old. The electrocardiograms taken at that time are not very different from those reproduced, which were made seven years later. When last seen, this young man was working and was free of symptoms. Note that the ventricular complexes of the unipolar left arm lead are like those of Lead V_5.

Persistent RS-T Displacement.—The electrocardiograms reproduced in Fig. 25 are those of a man, aged 73 years, who began to have anginal pain late in May, 1941, and developed myocardial infarction on June 11 of that year. Very pronounced RS-T displacement of the kind commonly seen in very recent anterior infarction was still present on Nov. 7,

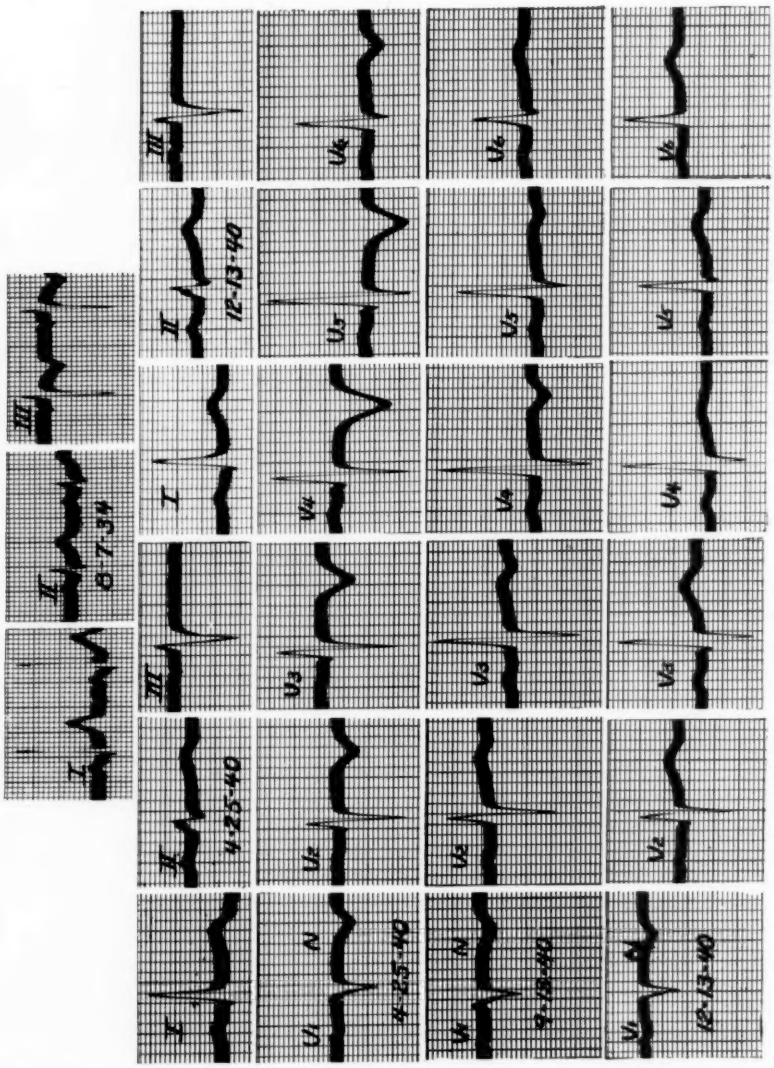

Fig. 22.—Anterior myocardial infarction; changes in the T waves only.

1941, when the first electrocardiogram was taken, and remained essentially unchanged on April 20, 1942. The patient developed congestive cardiac failure but had chest pain only during the earliest stage of his illness. Complete healing of the infarcted muscle must have taken place long before the last curves were made. Ordinarily, pronounced RS-T displacement of the kind in question persists for a few

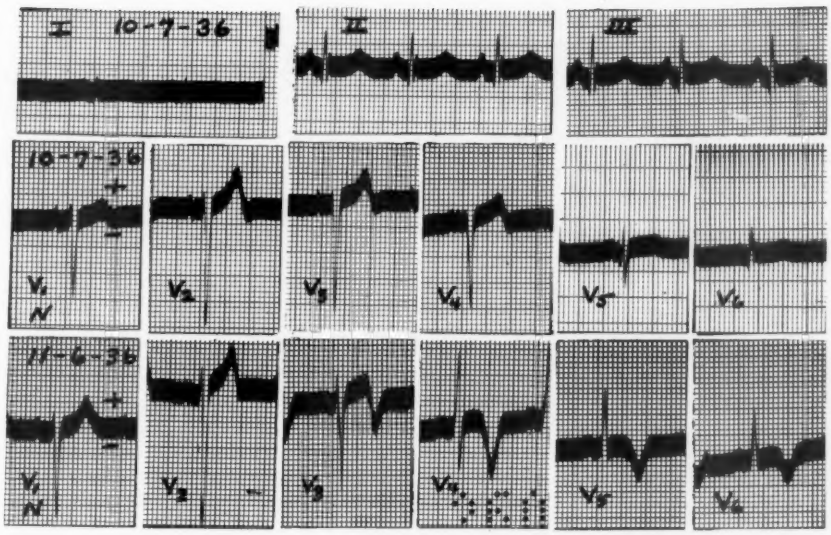

Fig. 23.—Anterior myocardial infarction; transient QRS changes.

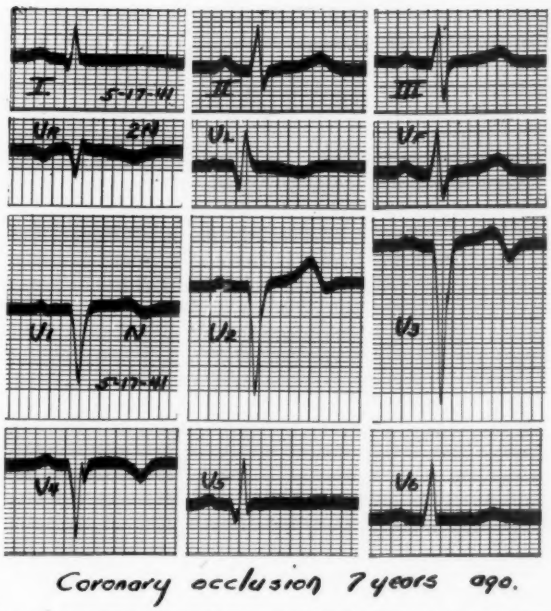

Fig. 24.—Anterior myocardial infarction; persistent changes in the QRS complex and residual changes in the T waves.

hours, or, at most, for a few days. Why it persists in rare instances for weeks or months is still a mystery. In three cases of this sort, one of which was observed by Langendorf,[20] a ventricular aneurysm was present, but it is possible that the association was due to chance. There

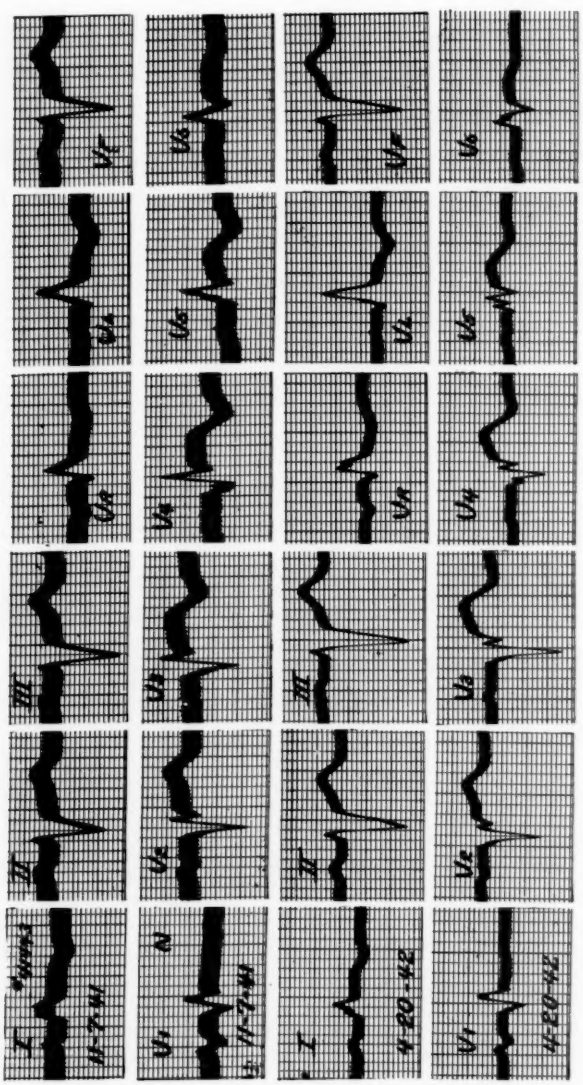

Fig. 25.—Anterior myocardial infarction: persistent RS-T displacement, incomplete right bundle branch block.

is no known reason why ventricular aneurysm should displace the RS-T junction or deform the RS-T segment in this way. In addition to RS-T displacement, both electrocardiograms display a QRS interval between 0.10 and 0.11 second in length, and late R waves in the leads from the right side of the precordium. These findings strongly suggest that incomplete right branch block was present.

Extensive Anterior Infarction.—In the three cases illustrated in Fig. 26, characteristic signs of infarction were present in all of the six precordial leads, or in all except the first. In such instances it must be assumed that the region involved is a very large one. The first patient was a woman, aged 48 years, who began to have symptoms typical of coronary thrombosis at 9:45 P.M. on Aug. 9, 1938. On the

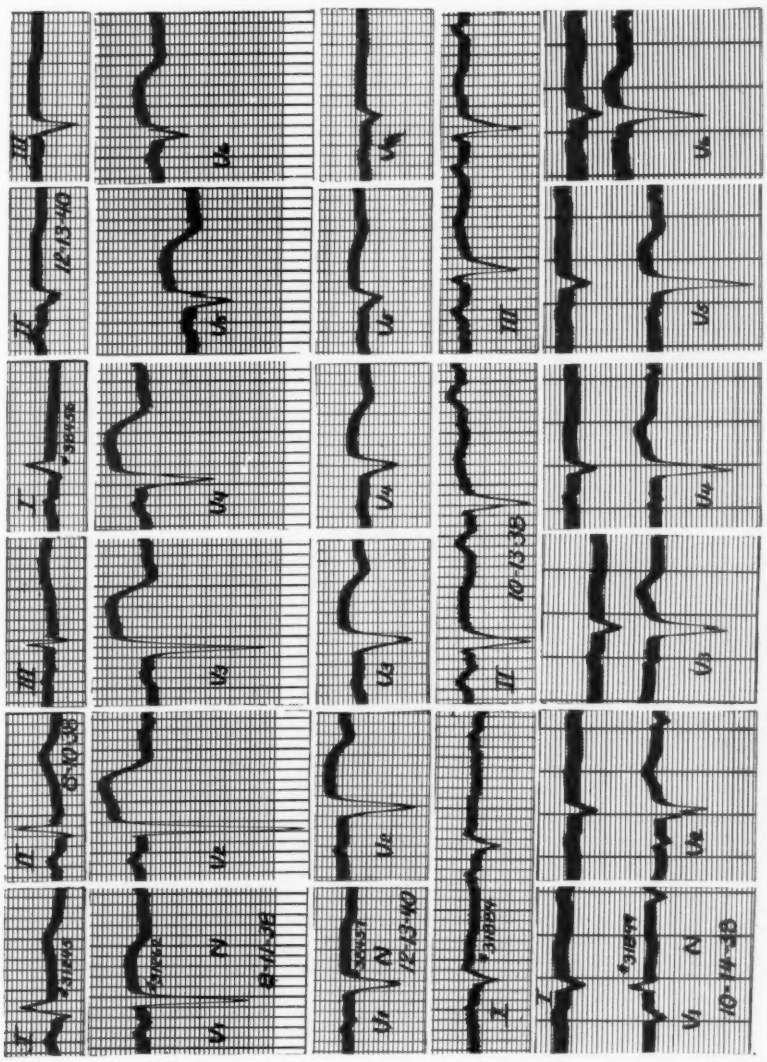

Fig. 26.—Three cases of extensive myocardial infarction.

next day, small QRS deflections, prominent Q waves, and upward displacement of the RS-T junction were present in Lead I. On August 11, the precordial electrocardiogram displayed large QS deflections and conspicuous upward RS-T displacement in all leads except V_1. The second patient was a man, aged 71 years, who began to have severe

pain in the chest at 9:45 P.M., on Dec. 10, 1940. On December 13, the changes in the precordial leads were almost identical with those that occurred in the case just described. Both patients recovered.

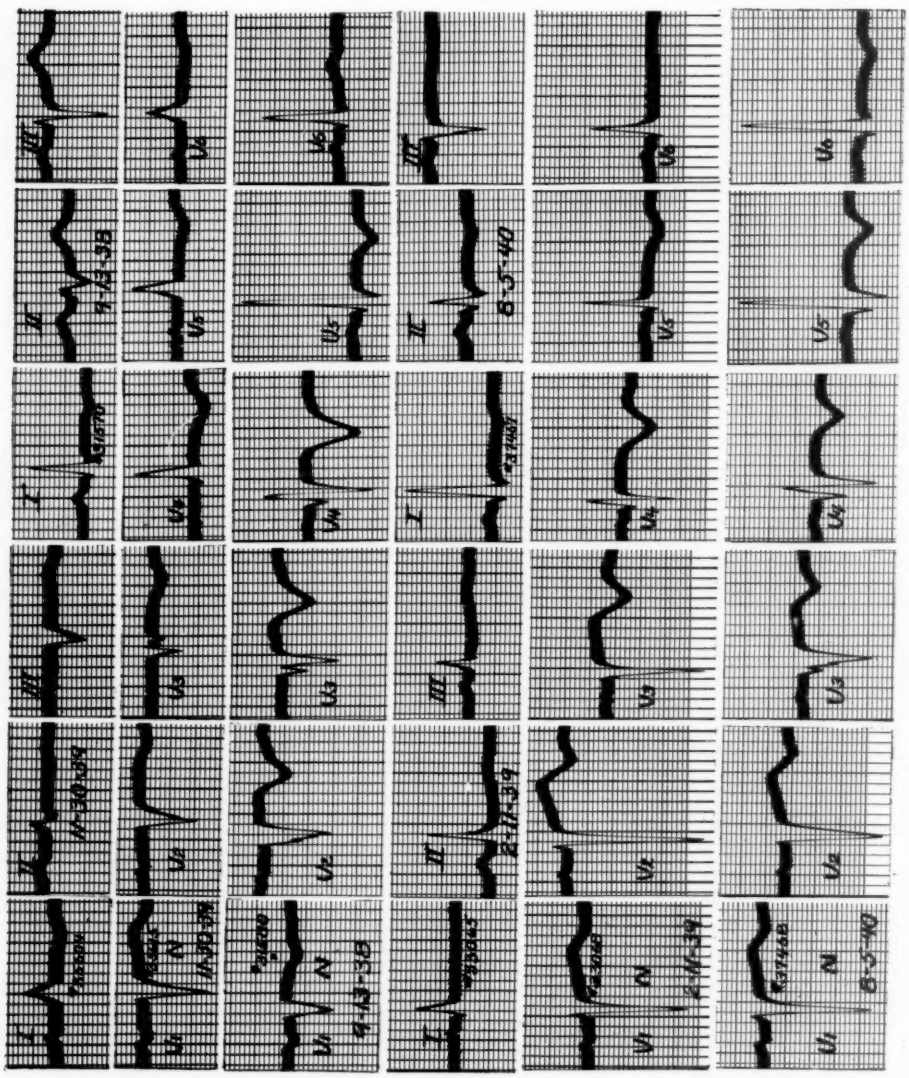

Fig. 27.—Four cases of anteroseptal infarction.

The third patient was a man, aged 48 years, who had severe attacks of anginal pain on Feb. 1, and on May 30, 1938. The first electrocardiogram was taken on Oct. 14, 1938. At that time there were very large Q deflections in Lead I and large QS deflections in the last five precordial leads. Probably because the infarct was an old one, no pronounced RS-T displacement or typical T-wave changes were present. The patient died on Oct. 16, 1938, and autopsy disclosed an infarct

measuring 9 by 10 cm., which involved the lower two-thirds of the anterolateral, and the lower one-third of the posterior, wall of the left ventricle. The cavity of this chamber was almost completely filled by a thrombus.

Anteroseptal Infarction.—In the four cases illustrated in Fig. 27, the diagnostic signs of infarction (characteristic QRS combined with characteristic RS-T or T-wave abnormalities) were confined to the leads from the right side of the precordium. Leads V_5 and V_6 display alterations in the T waves which are more or less typical but no unequivocal changes in the QRS complexes. Since the potential variations of the left arm are like those of the left side of the precordium in the majority of the cases of anterior myocardial infarction, the changes in the ventricular complexes of Lead I are as a rule no greater than those displayed by the ventricular complexes of Lead V_5. An electrocardiographic diagnosis of anterior infarction, therefore, cannot be made with certainty in cases of the kind under consideration unless leads from the right side of the precordium are employed. Since the potential variations of the infarcted region are referred to the right side of the precordium, we may assume that the anteroseptal wall of the left ventricle is involved.

The first patient was a man, aged 68 years, who developed myocardial infarction in September, 1939. The electrocardiogram, taken on November 30 of that year, shows notched QS deflections in Leads V_2 and V_3 and inversion of the T waves, not of the kind characteristic of infarction, in Leads I, V_3, V_4, V_5, and V_6. The ventricular complexes of Lead I closely resemble those of Lead V_6.

The second patient was a man, aged 57 years, who had a coronary accident about Sept. 1, 1938. The electrocardiograms, made on September 13, show characteristic changes in the T waves of Leads I, V_2, V_3, V_4, and V_5. Characteristic changes in the QRS complexes are confined to Leads V_2 and V_3. The ventricular complexes of Lead I are like those of Lead V_5.

The third patient was a woman, aged 48 years, who began to have symptoms typical of coronary thrombosis on Feb. 9, 1939. The electrocardiograms, taken on February 11, show signs diagnostic of infarction in Lead V_3 and typical T-wave changes in Lead V_4. The ventricular complexes of Lead I are like those of Lead V_6.

The fourth patient was a man, aged 59 years, who had a coronary occlusion on May 14, 1940. The electrocardiograms of Aug. 5, 1940, display signs diagnostic of infarction in Leads V_3 and V_4 and characteristic T-wave changes in Leads V_5 and V_6. The ventricular complexes of Lead I are like those of Lead V_6.

In normal subjects the R deflection steadily increases in height as the precordial electrode is moved from the first to the fourth position and

then decreases as it is moved farther to the left. The decrease in the height of R, and its eventual disappearance as the exploring electrode was moved across the right side of the precordium in a number of the cases just described, is a far more reliable sign of infarction than complete absence of this deflection in the first two or three precordial leads.

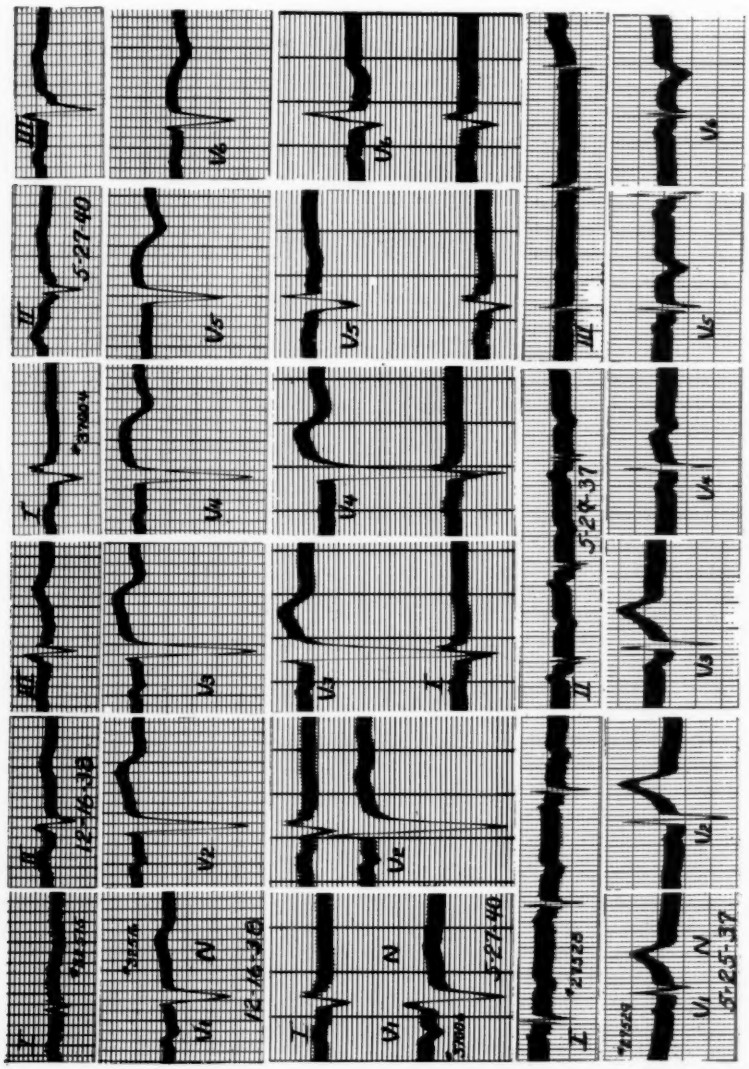

Fig. 28.—Two cases of anterolateral and one case of posterolateral infarction.

Anterolateral Infarction.—In the first two of the three cases illustrated in Fig. 28, the diagnostic signs of infarction in the chest leads are confined to the leads from the left side of the precordium, and it may be assumed that the anterolateral wall of the left ventricle was involved.

The first patient was a man, aged 70 years, who had a severe attack of anginal pain on July 6, 1938. The precordial electrocardiogram, taken on December 16 of the same year, displays signs diagnostic of infarction in Leads V_4 and V_5, and abnormally small R deflections associated with changes in the T complex in Lead V_6. In Lead I the QRS deflections are extremely small, and suggestive changes in the T waves are present.

The second patient was a man, aged 47 years, who was disoriented when admitted to the hospital, so that no history of his illness could be obtained. It was learned later that he had had anginal pain, but the time at which coronary thrombosis occurred could not be determined. The electrocardiogram displays deep Q deflections in Lead I and in Lead V_5, and the ventricular complexes of these leads are very much alike. There is also a rapid decrease in the size of the R deflection between Lead V_2 and Lead V_5. No characteristic modifications of the RS-T segment or T wave are present, probably because the infarct was an old one.

In infarcts of this kind, as a rule, there are changes diagnostic of infarction in the ventricular complexes of Lead I. Since the infarct involves the left upper margin of the heart, the potential variations at its epicardial surface are transmitted to the left arm.

The third case illustrated in Fig. 28 belongs to a different group and will be referred to later.

High Lateral Infarction.—The electrocardiograms reproduced in Fig. 29 are those of a man who was under observation off and on from September, 1926, until his death on Jan. 19, 1942. In the autumn of 1934, he began to have mild anginal pain on exertion after meals, and at 3 o'clock on the morning of Aug. 18, 1935, he developed symptoms characteristic of coronary thrombosis. The electrocardiogram taken on the following day presents small QRS deflections, deep Q waves, and sharply inverted T waves in Lead I. The precordial electrocardiogram taken at the same time, which is not reproduced, is not definitely outside normal limits, but the R and T waves of Leads V_1 and V_2 are unusually prominent. The patient had no more anginal pain and got along very well until June 3, 1940, at 12:30 P.M., when a second coronary accident occurred. The electrocardiogram taken two days later is very similar to that of 1935 except that the QRS interval is a little longer. Precordial leads were not used on this occasion. In October, 1941, paroxysmal nocturnal dyspnea began to occur, and in January, 1942, the patient entered the hospital with the symptoms and signs of congestive cardiac failure, and attacks of substernal oppression.

On January 13, the limb leads showed a QRS interval measuring approximately 0.11 second, left axis deviation, and inverted T deflections in Lead I. The precordial curves of the next day present a very small R deflection in Lead V_2 and prominent Q waves in Lead V_3, but no other changes which suggest infarction. The third attack of severe

anginal pain began at 7 A.M., on January 15. On January 17, right bundle branch block was present. The precordial leads then showed changes characteristic of this conduction defect and small bizarre QRS deflections in Lead V_3.

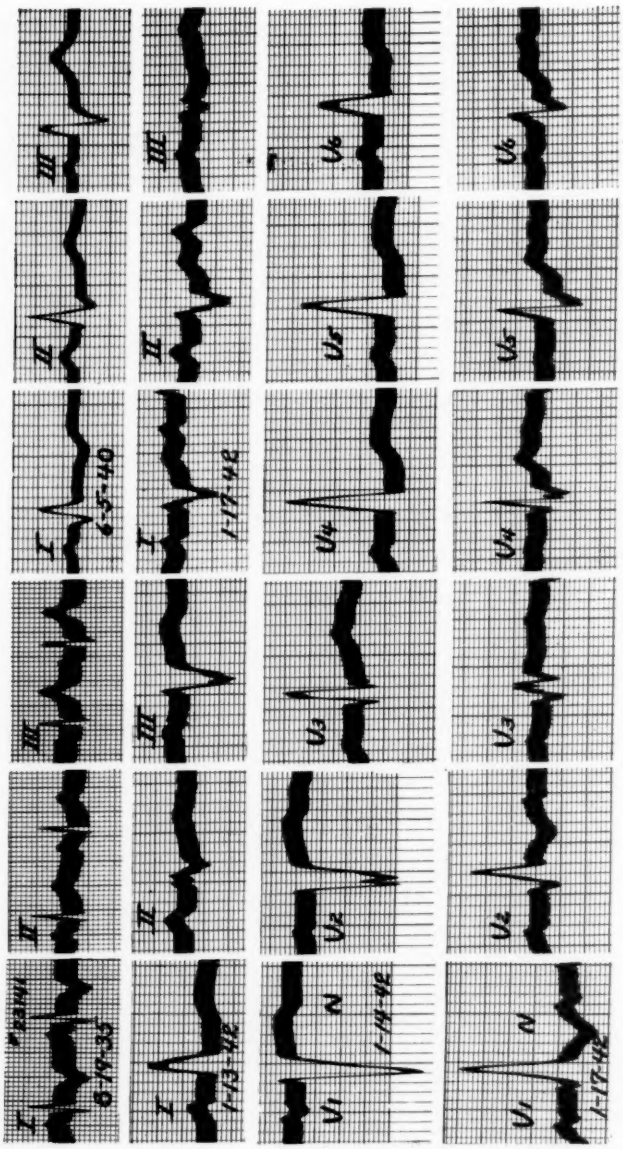

Fig. 29.—High lateral infarction (see text).

The autopsy disclosed a very large thrombus covering the apical two-thirds of the inner aspect of the anterior wall of the left ventricle. Beneath this clot the endocardium was grayish-white in color, and near the base of the ventricle it was about one millimeter thick. Mottled grayish-

pink to bluish-red areas were scattered through the anterior wall of the left ventricle, the septum, and the apical parts of the right ventricle, which also contained a thrombus. The left coronary artery was blocked by a fresh clot near its origin. In the posterolateral wall of the left ventricle near its base there were extensive grayish-white to grayish-yellow areas which were thought to represent old myocardial infarction. The infarct responsible for the electrocardiographic changes observed in 1935 and 1940 apparently involved this region. We have seen only one other instance in which the limb leads showed signs diagnostic of anterior infarction and the precordial leads did not.

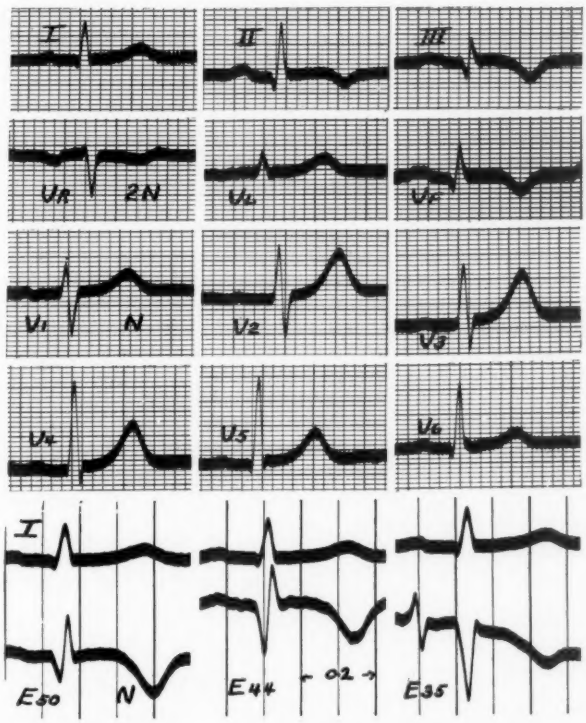

Fig. 30.—Plain posterior infarction. In this as in other figures the symbol *E* is used for unipolar esophageal leads. The figure which follows this symbol gives the distance (in centimeters) of the esophageal electrode from the nostrils.

Plain Posterior Infarction.—The man, aged 45 years, whose electrocardiograms are shown in Fig. 30, was referred to us for laboratory studies only. He had symptoms typical of coronary thrombosis about one month before these curves were taken. The deep Q waves and sharply inverted T waves of Leads II and III indicate that there was a recent infarct on the posterior wall of the heart. Note that the potential variations of the outer surface of the infarct were transmitted to the left leg. The precordial leads show no significant abnormalities, but it will be observed that, in Leads V_1 and V_2, the R deflections and T waves are unusually tall. Characteristic signs of infarction are present

in the leads from the ventricular levels of the esophagus (Leads E_{44} and E_{50}). In the lead from the auricular levels of the esophagus (Lead E_{35}), there is a large diphasic auricular complex, and the ventricular complex consists of a large QS deflection followed by an inverted T wave. Electrocardiograms of this kind are obtained from the auricular levels of the esophagus in normal subjects.[21] The exploring electrode is close to the auricular wall, which accounts for the character of the auricular complex, and also opposite the great valvular orifices at the base of the ventricles so that the negativity of the ventricular cavities is transmitted to it. Large Q or QS deflections in leads from this region have no significance.

In the earliest stages of infarction of the posterior wall of the heart, downward displacement of the RS-T junction is usually present in the precordial leads. In leads from the ventricular levels of the esophagus, the displacement is upward.[21]

Posterolateral Infarction.—The last of the three patients whose electrocardiograms are reproduced in Fig. 28 was a physician, aged 42 years, who had a coronary accident on March 18, 1937. The limb leads, taken on May 25 of the same year, display inverted T waves in Leads I and II and small QRS deflections with prominent Q waves in Leads II and III. There is also a small Q deflection in Lead I. The changes in the T waves resemble those found in anterior, and the changes in the QRS complex those found in posterior, infarction. In the precordial curves, the significant abnormalities are in Leads V_5 and V_6, which show prominent Q and sharply inverted T waves. It will be noted, however, that in the leads from the right side of the precordium, the R and T deflections are unusually prominent.

Another electrocardiogram of the same sort is reproduced in Fig. 31. The patient was a man, aged 54 years, who had symptoms typical of coronary thrombosis about one month before the electrocardiographic study was made. In this instance, unipolar leads from the left posterior axillary line, from the left infrascapular region, and from the ventricular levels of the esophagus were taken, and all of these show prominent Q and sharply inverted T waves. Similar but less characteristic changes are present in the leads from the left side of the precordium (Leads V_5 and V_6). There can be little doubt that the infarct involved the posterolateral wall of the heart. Note that here also large Q and inverted T waves occur in the unipolar left leg lead. Not all cases in which there are sharply inverted T waves in Lead I and abnormally large Q waves in Leads II and III are examples of posterolateral infarction. This electrocardiographic pattern in the limb leads may be produced by the simultaneous presence of two infarcts, an old lesion on the posterior, and a more recent one on the anterior, wall of the heart. It may also occur in anteroseptal infarction in which, perhaps because of some peculiarity in the position of the heart or because there is more

involvement of the septal wall of the left ventricle than is usual, the potential variations of the central part of the infarcted ventricular wall are sometimes transmitted to the left leg.

Posteroinferior Infarction.—The electrocardiograms reproduced in Fig. 32 are those of a man, aged 53 years, who had symptoms typical of coronary occlusion on Dec. 19, and Dec. 23, 1941. The curves taken

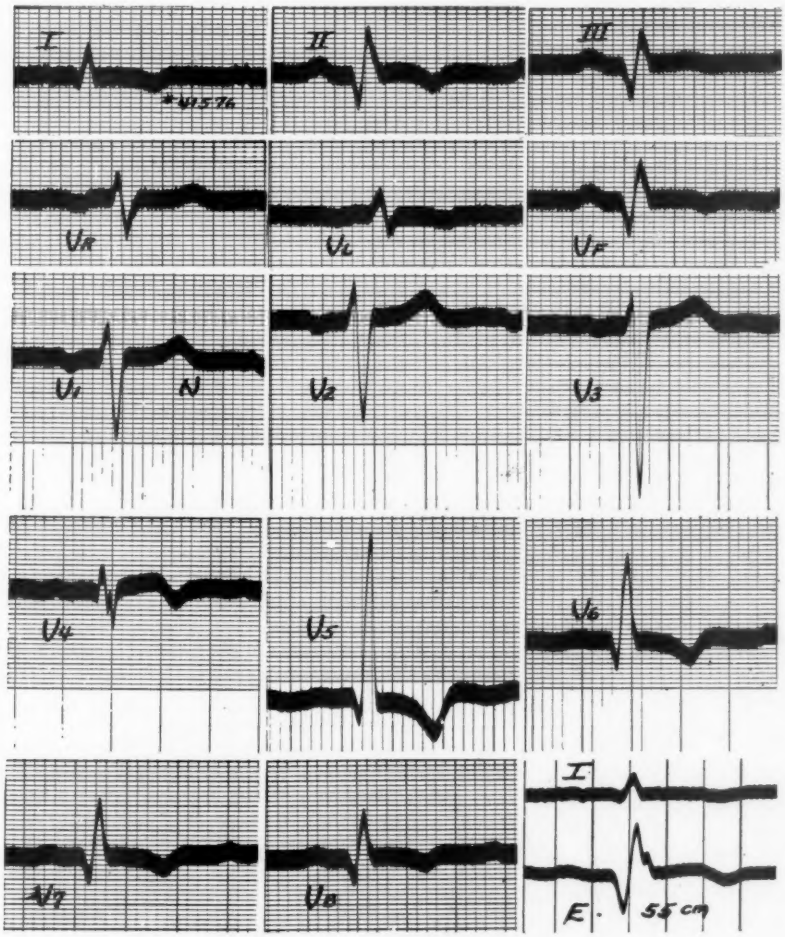

Fig. 31.—Posterolateral infarction.

on December 26 show upward displacement of the RS-T junction, sharply inverted T waves and prominent Q deflections in Leads II, III, and V_F, and complete atrioventricular block, which was transient. Signs diagnostic of infarction are present in the unipolar lead from the tip of the ensiform cartilage (Lead V_E), but in none of the usual precordial leads. It will be noted that, in this instance, the R and T waves are not unusually prominent in the leads from the right side of the precordium. On the contrary, no R wave is present in Lead V_1, and the R wave in Lead

V_2 is unusually small. In some cases of this sort, slight upward displacement of the RS-T junction occurs in Lead V_1 in the early stages of infarction.

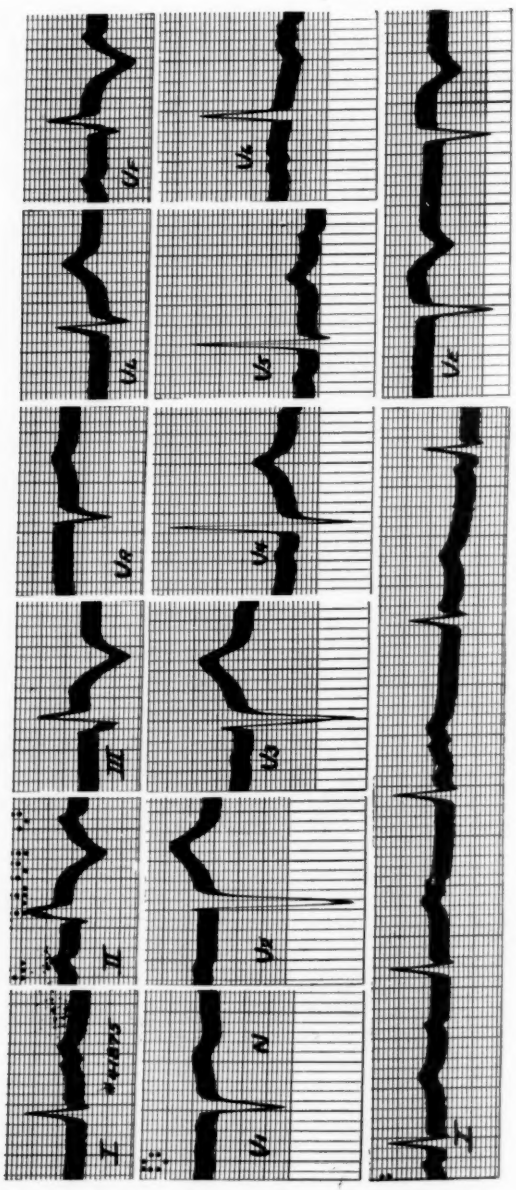

Fig. 32.—Posteroinferior infarction.

Signs of Posterior Infarction in Limb Leads and of Anterior Infarction in the Precordial Leads.—We have seen only one case of the kind illustrated in Fig. 33. The patient, a man aged 68 years, had a coronary accident on March 31, 1935, while he was under treatment for prostatic hypertrophy. He died three days later, but permission for an autopsy

could not be obtained. No symptoms referable to the heart had occurred previous to this fatal illness. The limb leads show pronounced upward displacement of the RS-T junction and prominent Q deflections in Leads II and III and in precordial Lead V_3. There is, in addition, conspicuous RS-T displacement without characteristic alterations of the QRS complex in Leads V_2 and V_5. Leads V_4 and V_6 were not taken.

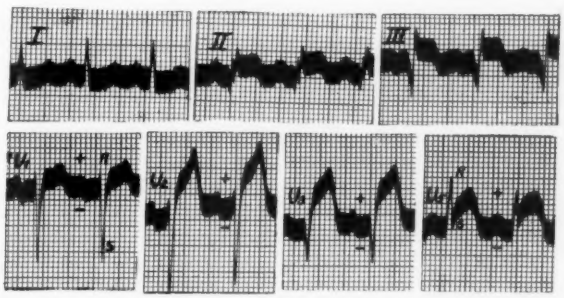

Fig. 33.—Signs of posterior infarction in the limb leads and of anterior infarction in the precordial leads. (After Wilson.[22] Reproduced with the permission of the Macmillan Company, New York.)

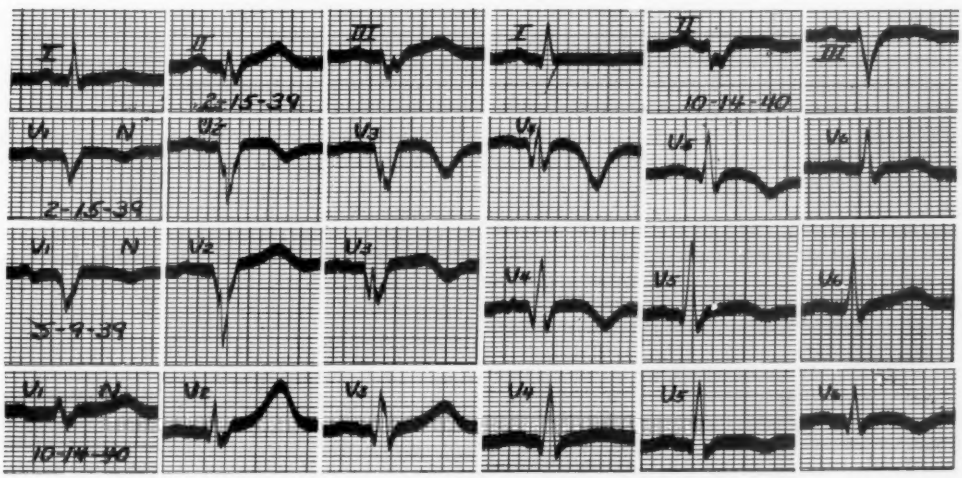

Fig. 34.—Anteroseptal followed by posterolateral infarction.

The character of the electrocardiographic changes precludes the possibility that there were two infarcts differing in age. Nor does it appear consistent with the presence of a single infarct extending from the posterior wall of the heart around the left margin onto the anterior wall, for the most striking changes in the precordial leads are in the middle of the series. We are not able to explain these findings satisfactorily, but may point out that apical infarction might give rise to electrocardiographic changes of this sort if the heart were in the vertical position.

Old Anteroseptal and Recent Posterolateral Infarction.—The electrocardiograms reproduced in Fig. 34 are those of a man, aged 52 years, who had symptoms characteristic of infarction on Dec. 18, 1938, and

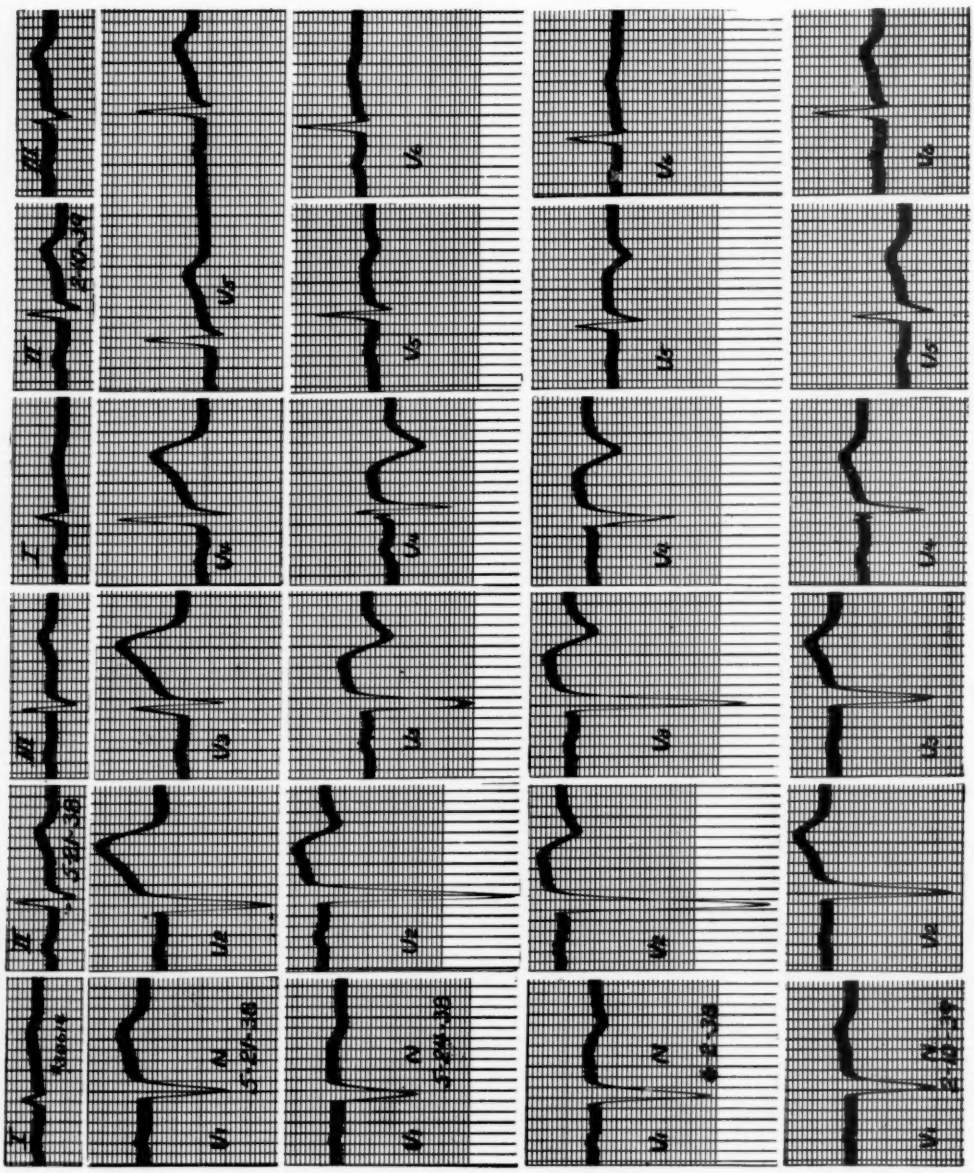

Fig. 35.—Serial electrocardiograms in a case of anteroseptal infarction.

made an uneventful recovery. On Aug. 29, 1940, he had a second attack of severe anginal pain. On this occasion he was examined at his home and the cardioscope disclosed very pronounced upward RS-T displacement in Leads II and III.

The electrocardiograms taken two months after the first attack show prominent Q deflections but no characteristic T-wave changes in Leads II and III. The precordial curves of the same date display signs diagnostic of infarction in Leads V_2, V_3, and V_4, and sharply inverted T waves in Lead V_5. Note that the ventricular complexes of Lead I resemble those of Lead V_6 which are in no way abnormal. The infarct was, then, of the anteroseptal variety. We have already mentioned that infarcts of this kind may give rise to prominent Q deflections in Leads II and III. After the second infarction, sharply inverted T waves appeared in the complexes of Lead V_6 which had previously escaped modification, and initial R deflections were present in Leads II and III. At the same time, conspicuous R waves were found in the leads from the right side of the precordium in which only embryonic R deflections had previously been present. Note, however, that the resurgent R waves are preceded by Q deflections in Leads V_2, V_3, and V_4. Observe also the large size of the T waves in Leads V_1, V_2, and V_3, in which deeply inverted T waves were present after the first coronary accident. The second infarct was, then, of the posterolateral kind.

We were able to make a more detailed study of another case in which the same series of events occurred. The patient was a man, aged 48 years, who had his first coronary thrombosis on May 21, 1938. The first electrocardiogram was taken about two hours after the onset of characteristic symptoms (Fig. 35). The limb leads showed no significant changes, but there was very pronounced upward displacement of the RS-T junction in Leads V_2, V_3, and V_4. Three days later, the R deflections had disappeared in Leads V_1, V_2, and V_3 and had become very small in Lead V_4, the RS-T displacement had begun to subside, and inversion of the terminal part of the T waves had developed in Leads V_1, V_2, V_3, V_4, and V_5. The ventricular complexes of Lead V_6 were not affected. In the course of the next year the T deflections regained their normal form, but the QRS changes persisted.

On March 5, 1942, the patient, who had been well for nearly three years, began to have new attacks of severe anginal pain. He was admitted to the hospital, but at first the electrocardiogram showed only the residual changes which dated from his first infarction (Fig. 36). On March 11, however, he developed clear signs of posterior infarction. In the extremity curves, these consisted of pronounced upward displacement of the RS-T junction and prominent Q deflections in Leads II and III. In the precordial electrocardiogram, inverted T waves eventually developed in the complexes of Lead V_6, which had escaped in the first attack, and small R waves appeared in Leads V_1, V_2, and V_3. In these same leads the T waves became larger than they had been before.

Anterior Infarction Plus Right Bundle Branch Block.—When anterior infarction produces right bundle branch block, modifications of the electrocardiogram that can be regarded as diagnostic of infarction are relatively rare in the limb leads. Displacement of the RS-T junction and

more or less characteristic changes in the T waves may be present, but, when the area of the QRS complex is large, they are often obscured by the alterations in the T complex due to the block. In the precordial leads, on the other hand, entirely characteristic modifications of the QRS

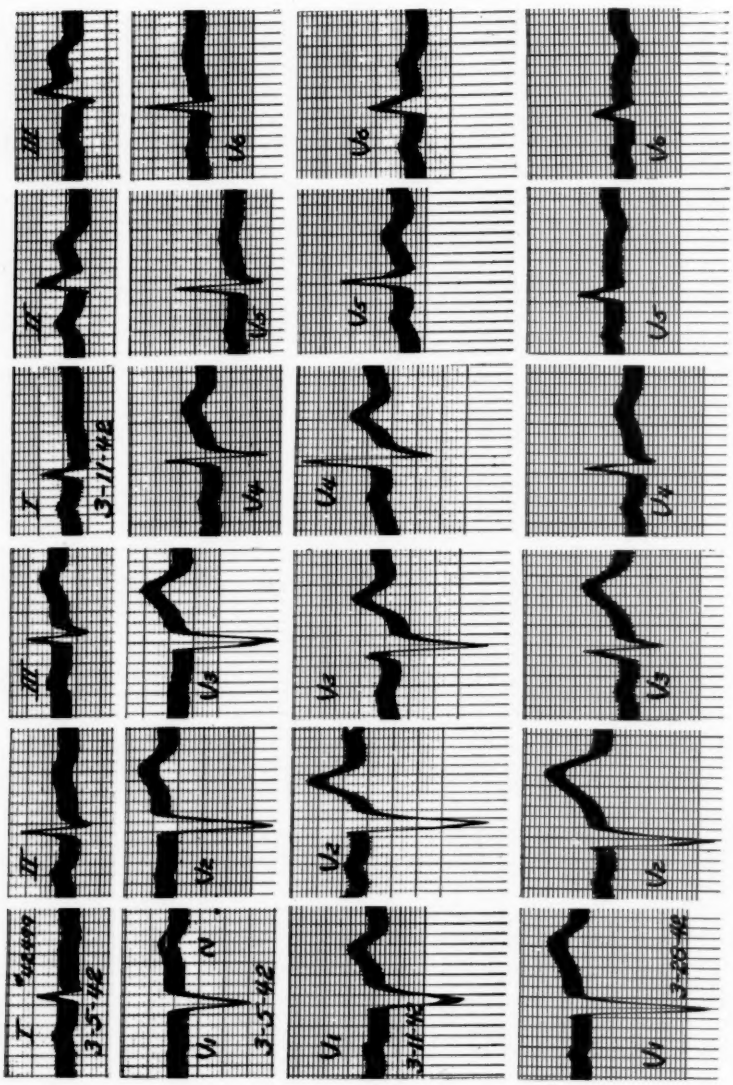

Fig. 36.—Serial electrocardiograms showing posterolateral infarction following anteroseptal infarction. (From the same case as Fig. 35.)

and T deflections are usually present. We have studied this problem experimentally by producing anterior infarction and right bundle branch block in dogs, and there are no essential differences between this animal and man, either as regards the character of the changes in the ventricular complexes of the limb leads, or as regards the changes of the ventricular deflections of precordial leads.

The electrocardiograms reproduced in Fig. 37 are those of a man, aged 37 years, who had severe attacks of anginal pain on July 26 and 28, 1938. Two days after the last attack, a pericardial friction rub was heard. The patient died on Sept. 18, 1938, and autopsy disclosed thrombosis of the anterior descending coronary artery and a very large anterior infarct over which the pericardium had become adherent. Liquefaction necrosis of the central part of the infarct had taken place.

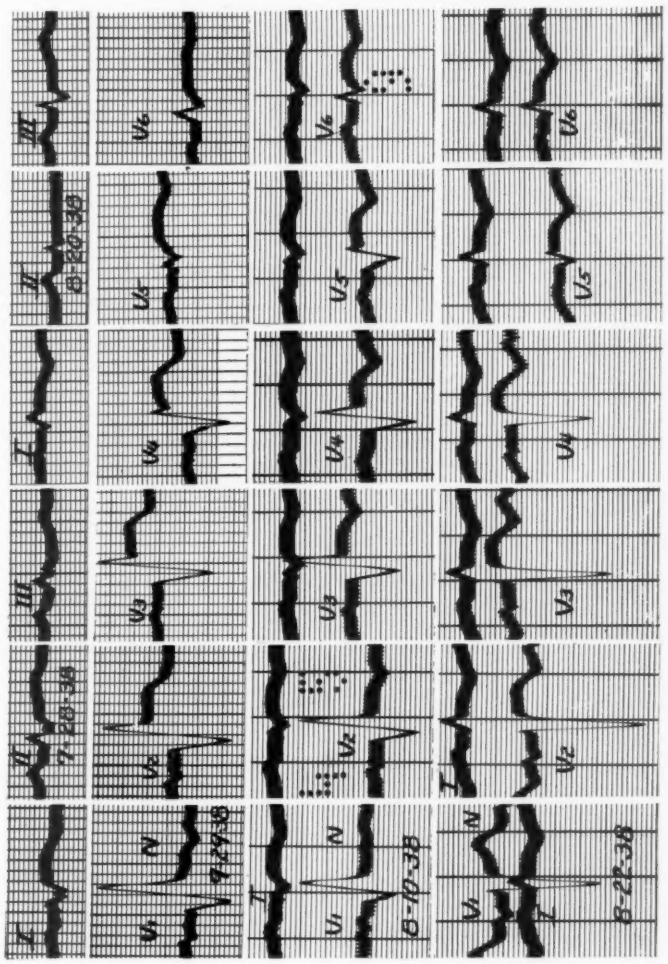

Fig. 37.—Anterior infarction complicated by transient right bundle branch block.

The limb leads, taken on July 28, show small broad QRS complexes and slight upward displacement of the RS-T junction in Lead I. The QRS interval measures approximately 0.12 second. The precordial curves taken on the following day are characteristic of anterior infarction complicated by right bundle branch block. The presence of the block is indicated by the length of the QRS interval, the very late R waves in Leads V_1, V_2, and V_3, and the broad S waves in Lead V_6. The small

initial R deflections which occur in the leads from the right side of the precordium in uncomplicated right bundle branch block are absent. The presence of the infarct is indicated by the very large Q deflections in Leads V_1, V_2, V_3, and V_4, the small bizarre QRS deflections in Lead V_5, and pronounced upward displacement of the RS-T junction in Leads V_2, V_3, and V_4. The precordial curves, taken on August 10, are not essentially different in general outline, but the RS-T displacement is not so great and the end of the T wave is slightly inverted in Leads V_2 to V_6 inclusive.

The electrocardiograms, taken on August 22, are very different. The QRS interval is normal, and small QRS deflections, prominent Q waves, and sharply inverted T waves are present in Lead I. In the precordial leads, the R deflection decreases from Lead V_1 to Lead V_4 where it is absent, and there are abnormally large Q deflections in Lead V_5. Displacement of the RS-T junction and inversion of the end of T are present in Leads V_2 to V_6. It is noteworthy that, although initial R waves were not present in Leads V_1, V_2, and V_3 so long as the branch block persisted, they appeared when normal intraventricular conduction was re-established. It should also be noted that the S waves which follow these small initial R deflections are much deeper than the Q waves present in the same leads during block. These initial R waves must evidently be ascribed to forces produced by activation of the free wall of the right ventricle, and the deep S waves that follow them, at least in part, to the activation of septal muscle from the right side.

Another example of anterior infarction plus right bundle branch block is illustrated in Fig. 38. The patient was a man, aged 56 years, who had a coronary thrombosis, either on Sept. 23 or on Oct. 3, 1938. The first electrocardiogram, taken before he had had anginal pain, is normal. After the coronary accident, the limb leads disclosed the presence of right branch block but showed no changes characteristic of myocardial infarction. The precordial curves, on the other hand, are characteristic of both of these conditions.

Posterior Infarction Plus Right Bundle Branch Block.—The electrocardiograms reproduced in Fig. 39 are those of a man, aged 53 years, who began to have symptoms characteristic of coronary thrombosis at 9 A.M. on April 30, 1941. The electrocardiograms, taken on May 27, 1941, display large Q waves in Leads II and III, and sharp inversion of the end of T in the latter. The QRS interval measures about 0.14 second and there is a broad S wave in Lead I. The precordial electrocardiogram is characteristic of right bundle branch block. The conspicuous Q waves and T-wave changes in Lead V_6 suggest that the marginal parts of the infarct involved the lateral wall of the left ventricle. In the cases we have observed, QRS changes in the limb leads characteristic of posterior infarction have not been obscured by the presence of right branch block.

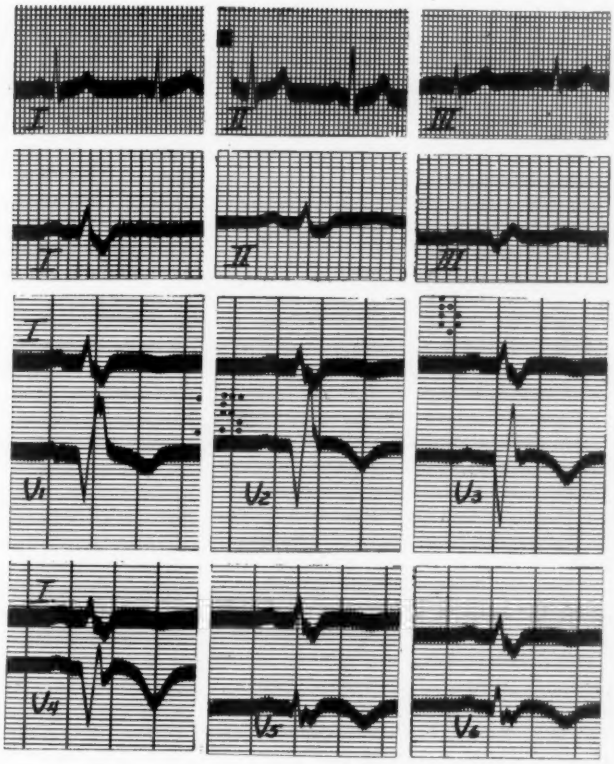

Fig. 38.—Anterior infarction complicated by right bundle branch block.

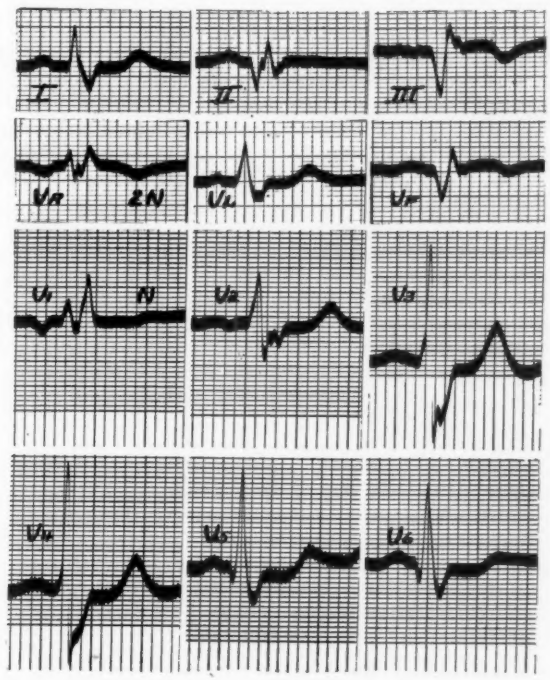

Fig. 39.—Posterior infarction complicated by right bundle branch block.

Myocardial Infarction Complicated by "Arborization" Block.—The electrocardiograms reproduced in Fig. 40 are those of a man who, after nine years of hypertension, developed myocardial infarction on Aug. 28, 1941. In the electrocardiograms of May 5, 1942, the limb leads display a QRS interval of about 0.14 second, deep, broad Q waves followed by

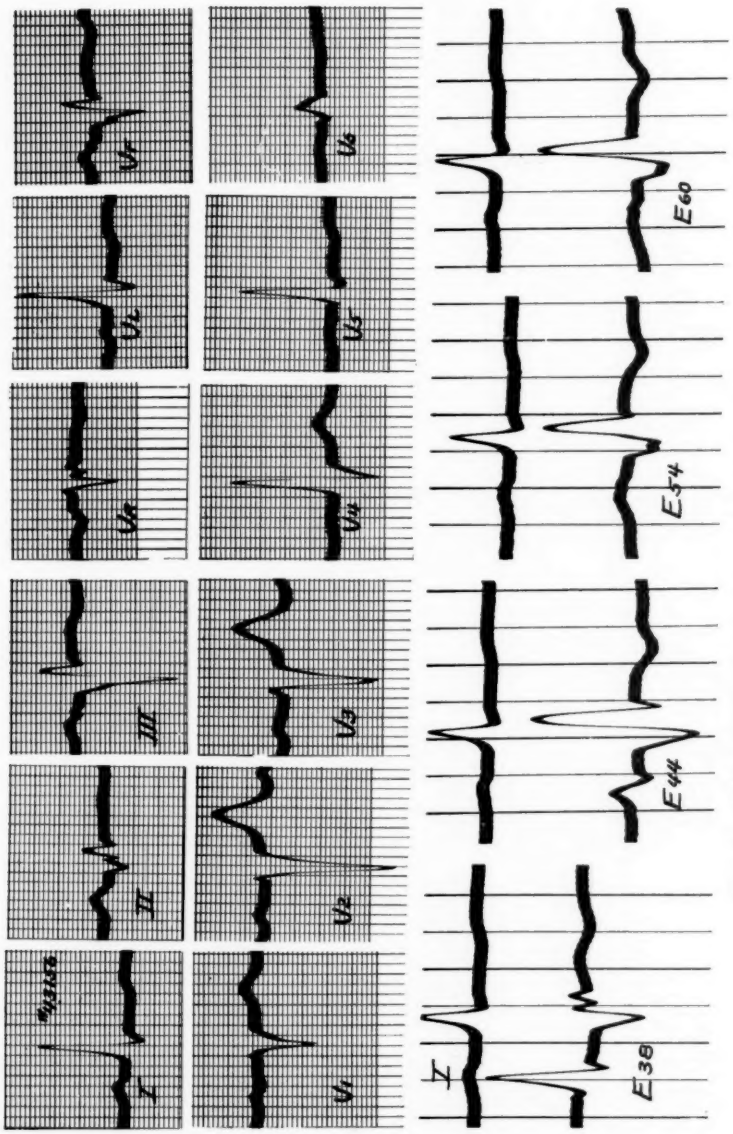

Fig. 40.—Posterior infarction complicated by "arborization" block.

late R waves in Leads II and III, and conspicuous S deflections in Lead I. This electrocardiographic pattern is very similar to that shown in Fig. 39, and posterior infarction complicated by right branch block was suspected. The precordial electrocardiogram, however, is incompatible

with the presence of this conduction defect, and shows no changes diagnostic of infarction; nor is it characteristic of left branch block. The leads from the ventricular levels of the esophagus (E_{44}, E_{54}, and E_{60}) present very broad, notched Q waves and very late, tall R deflections. It seems probable, therefore, that the infarct involved the subendocardial muscle on the posterior wall of the heart, and not only permitted the negativity of the left ventricular cavity to be transmitted to its epicardial surface during the first part of the QRS interval, but also delayed the activation of less seriously injured outer layers of muscle, which gave rise to the late R deflection.

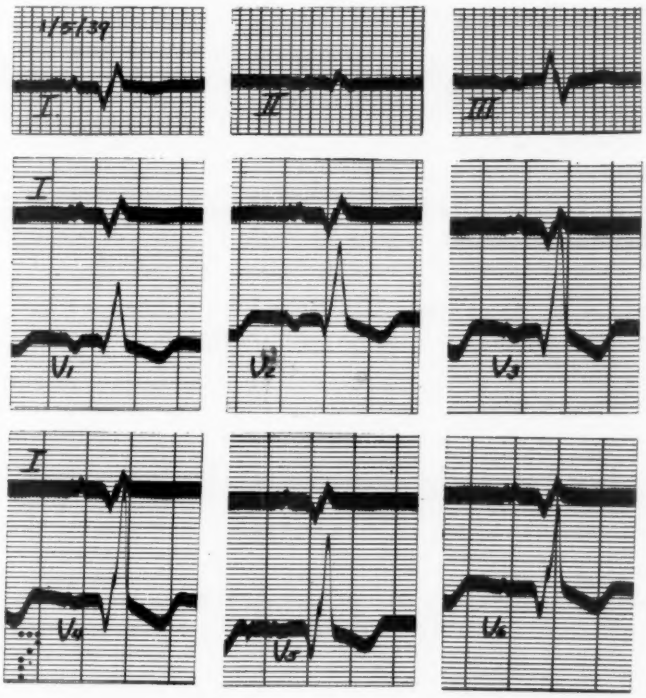

Fig. 41.—Anterior infarction complicated by "arborization block," by right bundle branch block, or by both.

The electrocardiograms reproduced in Fig. 41 are those of a man, aged 45 years, who had symptoms typical of coronary thrombosis, in January, 1938. The limb leads, taken a year later when the patient had congestive cardiac failure, display a QRS interval measuring between 0.11 and 0.12 second, small QRS deflections, and deep, broad Q waves in Lead I. The curves from the right side of the precordium are like those seen in right bundle branch block complicated by anterior infarction, but in this instance the curves from the left side of the precordium are of the same type. It will be noted that these ventricular complexes closely resemble the ventricular complexes of the esophageal electrocardiograms

reproduced in Fig. 40. In the case under consideration, leads from the ventricular levels of the esophagus yielded curves of the opposite type; the QRS complex of these tracings is diphasic and consists of an R wave followed by an S deflection of approximately equal size. It may be that these electrocardiograms represent right bundle branch block complicated by anterior infarction in which there is extreme displacement of the transitional zone. They are, however, more suggestive of anterior infarction with involvement of the subendocardial muscle over a large area, complicated by delayed activation of more normal subepicardial muscle and, perhaps, by right branch block as well. It seems probable that, in some cases of old infarction, the Purkinje network is damaged locally by subendocardial sclerosis and that, as a result, there is a delay in the activation of such living muscle as may remain in the part of the ventricular wall affected. Oppenheimer and Rothschild[16] had such lesions in mind when they introduced the term "arborization" block, but we doubt very much that the criteria for the electrocardiographic diagnosis of this condition advanced by them are capable of distinguishing between bundle branch block and intraventricular block of other types.

Infarction Complicated by Left Bundle Branch Block.—When coronary thrombosis is complicated by left bundle branch block, the electrocardiogram rarely presents changes which can be considered diagnostic of myocardial infarction. Displacement of the RS-T segment and changes in the T wave may occur if the area of the QRS complex is small. When the area of the QRS complex is large, the alterations in the T complex due to infarction are likely to be obscured by those produced by the conduction defect. The presence of characteristic modifications of the QRS deflections in infarction almost always depends upon the transmission of the potential variations of the cavity of the left ventricle to the epicardial surface of the infarct and the adjacent parts of the body. When this cavity is negative throughout the QRS interval, as is the case when intraventricular conduction is normal and in right bundle branch block, large Q or QS deflections occur in those leads in which one electrode is placed on that side of the left ventricle on which the infarct lies, provided that the connections are made in such a way that negativity of this electrode is represented by a downward deflection. In left bundle branch block, the cavity of the left ventricle is positive at the beginning of the QRS interval, and, consequently, Q or QS waves do not occur in leads of the kind mentioned. Direct or semidirect leads from the infarcted wall or from the cavity of this chamber display diphasic QRS complexes consisting of an R followed by an S deflection. Ventricular complexes of this sort are not sufficiently distinctive to have diagnostic value. When the septum is infarcted, as well as the free wall of the left ventricle, the cavity of the left ventricle is initially negative because the negativity of the cavity of the right is transmitted to it. Under these circumstances, the electrocardiogram may display large Q

or QS deflections in leads from the left precordium. The presence of large Q waves in these leads in left bundle branch block should always lead to the suspicion that the ventricular septum is involved.

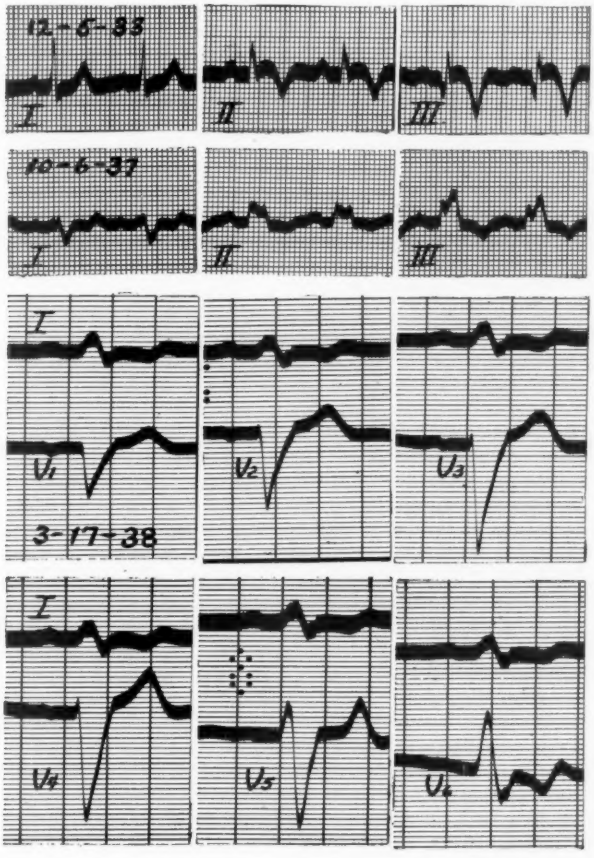

Fig. 42.—Posterior infarction complicated by left bundle branch block.

A case of infarction which was complicated by left bundle branch block is illustrated in Fig. 42. The patient was a man, aged 56 years, who had a coronary occlusion on Nov. 24, 1933. When he was first seen about ten days later, the limb leads showed the changes usually observed in posterior infarction. Except for inversion of the T waves in Lead V_6 the precordial leads were negative. A week later, the patient developed transient intraventricular block with ventricular complexes similar to those observed in 1937 and 1938 (see Fig. 42). The area of the QRS group was small, and the block did not abolish the inverted T waves in Leads II and III. It did abolish the prominent Q waves in these leads. These curves have been published (Wilson,[22] Fig. 78). When the patient returned in 1937, the intraventricular block was again present and it persisted. The ventricular complexes of the standard leads are of the

kind ascribed to right bundle branch block, but the precordial leads indicate that the conduction defect was in the left branch of the His bundle instead of the right. The heart was in the vertical rather than in the horizontal position. The QRS complexes of Lead V_6 are diphasic and, as regards their general outline, of the sort obtained by leading directly from the surface of an infarct of the left ventricular wall when left branch block is present. But QRS deflections of this kind may occur in Lead V_6 merely because the transitional zone is shifted unusually far to the left. They are not sufficiently distinctive to be helpful in the diagnosis of infarction. A case of septal infarction plus left bundle branch block is described in the article to which we have already referred (see Fig. 82 of that article).

In conclusion, we may say that we feel certain that, in the long run, unipolar precordial leads will be found superior to precordial leads of other kinds. They are the best available substitute for unipolar direct leads from the anterior surfaces of the ventricles. They are not directly influenced by the potential variations of the extremities; this makes them valuable in the analysis of electrocardiographic patterns in the standard limb leads with which we have long been familiar.

We must add that many of the views expressed here must be regarded as tentative. There are still many problems to be solved. We do not know exactly what degree of correlation may exist between the electrocardiographic position and the anatomic position of the heart. We have, as yet, very little information as to the effect of the latter upon the precordial electrocardiogram. The factors that determine the location and breadth of the transitional zone are still obscure. It is desirable that the effects of preponderant hypertrophy of the right and of the left ventricle upon the form of the precordial deflections be studied experimentally. It is still impossible to diagnose the lesser grades of this condition with any certainty. We need to have a better idea as to what parts of the heart's surface play the most important role in determining the potential variations of the extremities and other points on the body distant from the heart. We must study more carefully the electrocardiographic changes produced by combinations of lesions, such as right ventricular hypertrophy and right bundle branch block, and by conduction defects which delay the activation of local regions of muscle, particularly in myocardial infarction ("arborization block"). We must determine more exactly what the different electrocardiographic patterns seen in infarction mean in terms of the size of the infarct, its location, and the character of the changes in the muscle involved.

We feel sure that the future will see a great increase in the use of precordial and other special leads, and that it will bring us far greater knowledge of the electrocardiogram than we now possess.

REFERENCES

1. Lewis, T., and Rothschild, M. A.: The Excitatory Process in the Dog's Heart. Part II. The Ventricles, Phil. Trans. Roy. Soc. Lond. Series B. 206: 181, 1915.

2. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Distribution of the Action Currents Produced by Heart Muscle and Other Excitable Tissues Immersed in Extensive Conducting Media, J. Gen. Physiol. **16**: 423, 1933.
3. Cole, K. S., and Curtis, H. J.: Electric Impedance of Squid Giant Axon During Activity, J. Gen. Physiol. **22**: 649, 1939.
4. Wilson, F. N., Hill, I. G. W., and Johnston, F. D.: The Interpretation of the Galvanometric Curves Obtained When One Electrode Is Distant From the Heart and the Other Near or in Contact With Its Surface, AM. HEART J. **10**: 176, 1934.
5. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Potential Variations Produced by the Heart Beat at the Apices of Einthoven's Triangle, AM. HEART J. **7**: 207, 1931.
   Wilson, F. N., Johnston, F. D., Macleod, A. G., and Barker, P. S.: Electrocardiograms That Represent the Potential Variations of a Single Electrode, AM. HEART J. **9**: 447, 1934.
6. Eckey, P., and Fröhlich, R.: Zur Frage der unipolaren Ableitung des Elektrokardiogramms, Arch. f. Kreislaufforsch. **2**: 349, 1938.
7. Burger, R.: Ueber die herzferne Elektrode bei der semidirekten Ableitung; über die Nullpotentialelektrode von Wilson; über die Verwendung einer von der gesamten Körperoberfläche ableitenden Elektrode als indifferente Test-Elektrode, Cardiologia **3**: 56, 1939.
8. Burger, R., and Wuhrmann, F.: Ueber das elektrische Feld des Herzens. 2 Mitteilung; Die Darstellung des elektrischen Feldes des Herzens durch das "Diagramm der Potentialdifferenzen." Der Vergleich dieses Diagramms mit dem Vektordiagramm, Cardiologia **3**: 139, 1939.
9. Arrighi, F.: Personal communication.
10. Supplementary Report by the Committee of the American Heart Association for the Standardization of Precordial Leads, AM. HEART J. **15**: 235, 1938.
11. Kossmann, C. E., and Johnston, F. D.: The Precordial Electrocardiogram. I. The Potential Variations of the Precordium and of the Extremities in Normal Subjects, AM. HEART J. **10**: 925, 1935.
12. Goldberger, E.: A Simple Indifferent Electrocardiographic Electrode of Zero Potential and a Technique of Obtaining Augmented Unipolar Extremity Leads, AM. HEART J. **23**: 483, 1942.
13. Wilson, F. N., Johnston, F. D., Cotrim, N., and Rosenbaum, F. F.: Relations Between the Potential Variations of the Ventricular Surfaces and the Form of the Ventricular Electrocardiogram in Leads From the Precordium and the Extremities, Tr. A. Am. Physicians **56**: 258, 1941.
14. Kraus, F., and Nicolai, G.: Das Elektrokardiogramm des gesunden und kranken Menschen, Leipzig, 1910, Veit and Comp.
15. Wilson, F. N.: Concerning the Form of the QRS Deflections of the Electrocardiogram in Bundle Branch Block, J. Mt. Sinai Hosp. **8**: 1110, 1942.
16. Oppenheimer, B. S., and Rothschild, M. A.: Electrocardiographic Changes Associated With Myocardial Infarction, J. A. M. A. **69**: 429, 1917.
17. Hecht, H., Johnston, F. D., and Wilson, F. N.: Unpublished observations.
18. Johnston, F. D., Hill, I. G. W., and Wilson, F. N.: The Form of the Electrocardiogram in Experimental Myocardial Infarction. II. The Early Effects Produced by Ligation of the Anterior Descending Branch of the Left Coronary Artery, AM. HEART J. **10**: 889, 1935.
19. Wilson, F. N., Johnston, F. D., and Hill, I. G. W.: The Form of the Electrocardiogram in Experimental Myocardial Infarction. IV. Additional Observations on the Later Effects Produced by Ligation of the Anterior Descending Branch of the Left Coronary Artery, AM. HEART J. **10**: 1025, 1935.
20. Langendorf, R.: Personal communication to F. F. Rosenbaum.
21. Hamilton, J. G. M., and Nyboer, J.: The Ventricular Deflections in Myocardial Infarction. An Electrocardiographic Study Using Esophageal and Precordial Leads, AM. HEART J. **15**: 414, 1938.
    Nyboer, J.: The Normal and Abnormal Esophageal Electrocardiogram With Particular Reference to Myocardial Infarction, AM. HEART J. **22**: 469, 1941.
22. Wilson, F. N.: The Electrocardiogram in Diseases of the Coronary Arteries, Chapter XII in: Levy, R. L.: Diseases of the Coronary Arteries and Cardiac Pain, New York, 1936, The Macmillan Company.

TOXIC REACTIONS TO THE INTRAVENOUS INJECTION OF MERCURIAL DIURETICS

JACK WEXLER, M.D., AND LAURENCE B. ELLIS, M.D.
BOSTON, MASS.

ALTHOUGH it has been known for at least eleven years that sudden death may occur after intravenous injections of mercurial diuretics, it has been only within the past two years that widespread interest has arisen among physicians concerning these unfortunate accidents. In 1931, Wolf and Bongiorno[1] reported a case of sudden death of a 4-year-old child with nephrosis after the intravenous injection of 1 c.c. of salyrgan. In 1936, Cadbury[2] reported a fatality after the first injection of 0.6 c.c. of salyrgan into the jugular vein of a 5-year-old boy with nephritis. Collapse and death ensued within ten minutes. In addition, he cited instances of serious, nonfatal reactions to salyrgan in three adults with well-marked renal disease. The next year Greenwold and Jacobson[3] added two more cases of sudden death of children with nephrosis, one after 0.5 c.c., and the other after 1 c.c., of salyrgan, intravenously. In 1941, Tyson[4] observed one more fatal reaction in a 3-year-old nephrotic patient and a near fatality in a 27-year-old person with the same disease.

These papers, which appeared in a ten-year period, attracted little attention, probably because all of the fatalities occurred in very young children who were suffering from serious renal disease. However, in November, 1941, a letter was published in the *Journal of the American Medical Association*[5] citing four fatal reactions to mercupurin intravenously in patients with cardiac decompensation. The same cases were discussed in greater detail in a later communication.[6] At the same time a clinical study by Barker, Lindberg, and Thomas[7] added three more fatalities among cardiac patients and one in a 48-year-old patient with the nephrotic stage of chronic glomerulonephritis. In the last case, death occurred after the first injection. In all except one of these cases, death took place within five minutes after an intravenous injection of a mercurial diuretic (salyrgan or mercupurin).

The purpose of this communication is to add two more fatal reactions to mercupurin to the growing list, and, especially, to emphasize that nonfatal reactions of varying types and degrees of severity occur not uncommonly. The pathogenesis and the relation of these different types of nonfatal to fatal reactions will be discussed. No attempt has been

From the Thorndike Memorial Laboratory, the Second and Fourth (Harvard) Medical Services, Boston City Hospital, and the Department of Medicine, Harvard Medical School.

Received for publication March 15, 1943.

made to survey the total number of reactions which have occurred at the Boston City Hospital; indeed, this is impossible, as will be evident. Nevertheless, in the past sixteen months, two fatal and nine alarming nonfatal reactions to such medication have come to our attention, some of which we have personally observed.

FATAL REACTIONS

The first fatal reaction occurred in a 24-year-old white woman with congenital pulmonary stenosis who had chronic cardiac failure. This patient had previously received a total of 164 c.c. of mercupurin intravenously over a period of eight months, with fair diuretic results. As her general cardiac status deteriorated, the response to mercupurin became less favorable. The dose was, therefore, gradually increased from 2 c.c. until she was receiving 3 c.c. of mercupurin three times a week. This maintained her weight quite constant. After each injection this patient was apprehensive, and had dyspnea, slight tachycardia, and orthopnea which lasted one to two minutes. Within one to two minuter after the final intravenous injection of 3 c.c., which was given at a time when the patient was extremely ill, she became very dyspneic and cyanotic, and died within a few minutes. Post-mortem examination showed no immediate cause of death, but confirmed the diagnosis of congenital pulmonary stenosis. Cardiac sclerosis of the liver was also found, together with the usual pathologic accompaniments of congestive heart failure.

The second fatality occurred in a 27-year-old white woman with nephrosis. She had received thirteen previous intravenous injections of mercupurin with no objective untoward reaction, but on each occasion she expressed great dislike for the injection because of an extremely unpleasant sensation which she could not describe. Within thirty seconds after the final intravenous injection of 2 c.c., which was given when the patient had improved sufficiently to be ambulatory, she became unconscious and rigid. She had three generalized tonic convulsions within the next two to three minutes. The pulse could not be felt at the wrist and there were no audible heart sounds. There was marked pallor of the face. Gasping respirations occurred a few times, but cardiac function could not be restored by injecting stimulants into the heart and giving artificial respiration. At post-mortem examination no immediate cause of death could be found. The kidneys showed the pathologic changes of chronic "nephrosis," and there was marked fibrosis of the thyroid gland. There were no other significant post-mortem abnormalities.

NONFATAL REACTIONS

These have varied in severity, and may be divided into immediate and delayed reactions. All of these reactions occurred in patients with edema caused by heart disease of various kinds.

A. *Immediate Reactions.*—

1. The most benign of the immediate reactions is entirely subjective. The patient dreads the injection because of an unpleasant sensation, with no objective disturbances of any kind. These patients have no objection to routine venepunctures or other intravenous medication. These untoward symptoms are not uncommon, but their exact frequency cannot be ascertained because they may not be called to the attention of the attending physician, or their import is not appreciated at the time.

2. Transitory dyspnea was noted in two cases within a few minutes after the intravenous injection of mercupurin.

The first patient was a 45-year-old white man with rheumatic heart disease, mitral stenosis, and aortic regurgitation, and moderate right- and left-sided failure. The first injection of 1 c.c. of mercupurin caused a transitory feeling of tightness in his chest. Two to five minutes after a rapid injection of 2 c.c., which was given two days later, he became very dyspneic but improved without treatment in a few minutes. Two subsequent injections of 1 and 2 c.c., diluted with 10 c.c. of saline, were given without reaction.

The second patient was a 71-year-old woman with coronary heart disease and moderate failure. One to three minutes after 2 c.c. of mercupurin were given intravenously she became very dyspneic, but improved without treatment a few minutes later. She had received mercupurin on previous hospital admissions without reaction.

3. A more alarming reaction consists of apprehension, substernal discomfort, slight increase in respiratory and pulse rate, and orthopnea.

This was observed in a 46-year-old white woman with hypertensive and rheumatic heart disease and moderate failure. Two to five minutes after 1.8 c.c. of mercupurin she became dyspneic and apprehensive and complained of substernal oppression. There was no change in blood pressure. The pulse rate rose to 100 per minute. Fifteen minutes later she was improved without treatment. This patient had received numerous previous injections without reaction; no subsequent injections were given.

4. Moderate collapse, cyanosis, and sweating were observed in two cases, with bradycardia in one and tachycardia in the other.

The first was a 33-year-old white man with rheumatic heart disease, mitral stenosis and regurgitation, aortic regurgitation, and auricular fibrillation, who was convalescing from cardiac decompensation. An initial injection of 2 c.c. of mercupurin was given without reaction. Several days later a second injection was followed in two to five minutes by pallor, cyanosis, and profuse sweating. The pulse rate was slow and regular at 50 per minute. An electrocardiogram which was taken twenty minutes later, when the patient was improved, showed auricular fibrillation with periods of complete heart block and a ventricular rate of 50.

The second patient was a 58-year-old white woman with hypertensive and coronary heart disease and moderate failure. Two to five minutes after 2 c.c. of mercupurin she became very apprehensive, dyspneic, and cyanotic, and perspired profusely. The pulse rate was rapid and the heart sounds were of poor quality. She responded to the administration of morphine and oxygen. Milder reactions had previously been noted after the administration of mercupurin intravenously.

It seems clear that these various immediate reactions are similar in nature. They differ only in degree.

B. *Delayed Reactions.*—The delayed reactions generally occur one to two hours after the injection.

1. Typical asthmatic attacks one to two hours after mercupurin administration were observed in two cases.

The first patient was a 69-year-old white man who was suffering from syphilitic and coronary heart disease, with slight right-sided failure and chronic bronchitis; he had previously received several injections of mercupurin without reaction. Two hours after the last injection of 2 c.c. of mercupurin he had a chill and became cyanotic and markedly dyspneic. On examination, both lungs were filled with high-pitched expiratory râles and wheezes. There had been no previous attacks of asthma. He responded to adrenalin in about thirty minutes.

The second patient was a 62-year-old man with hypertensive and coronary heart disease and congestive failure who developed dyspnea, with typical asthmatic breathing, about two hours after a third dose of 2 c.c. of mercupurin; the first two had been given without reaction. Recovery occurred before treatment was instituted.

2. Pulmonary demea developed one to two hours after the injection in two cases.

The first patient was a 22-year-old man with rheumatic fever, rheumatic heart disease, mitral stenosis, and cardiac decompensation, who received 2 c.c. of mercupurin intravenously for the first time. About one-half hour later he suddenly developed acute pulmonary edema, which responded promptly to routine therapy, consisting of morphine, oxygen, and tourniquets.

The second patient was a 37-year-old white woman with rheumatic heart disease, mitral and aortic stenosis and regurgitation, and moderate heart failure, who was given 2 c.c. of mercupurin intravenously. One hour later she had a chill, followed in twenty minutes by pulmonary edema. Recovery was prompt. Numerous previous injections had caused no symptoms.

DISCUSSION

Immediate Reactions (Fatal and Nonfatal). 1. *Clinical Considerations.*—The composite clinical picture of the fatal reaction, as constructed from our observations and from the descriptions in the literature, is characterized by a marked fall in blood pressure, either cardiac

arrest, cardiac irregularity, and/or marked bradycardia, cyanosis or marked pallor of the face, dyspnea with irregular, often gasping, respiration, unconsciousness, and, occasionally, convulsions. Generally, cardiac arrest occurs before respiratory paralysis, and death ensues within five minutes after the start of the injection.

Immediate nonfatal reactions occurred in many of the patients who ultimately died after the intravenous injection of a mercurial diuretic. This has already been mentioned as occurring in our two fatal cases. Wolf and Bongiorno's[1] patient had a febrile reaction to each injection of salyrgan. One week prior to death this patient developed the usual febrile response, plus a morbilliform rash. This subsided, and, one week later, 1 c.c. of salyrgan was given intravenously, with a fatal outcome within one minute. One of the patients reported by Barker, et al.,[7] had essentially a "fatal type" of reaction, with cardiac arrest, after the thirteenth injection of 2 c.c. of mercupurin, but recovered spontaneously ten minutes later. Four months later a similar reaction followed 2 c.c. of salyrgan, with death within two minutes. Similarly, in three of the four cases reported by Brown, et al.,[6] reactions to mercupurin were noted prior to the final fatal reaction.

In each instance, with the possible exception of Wolf and Bongiorno's case, previous reactions were of the immediate type, and, when multiple, the reactions always followed the same pattern in any one patient.

2. *Pathogenesis.*—The pathologic physiology of fatal reactions in man is not known. Post-mortem examinations have failed to disclose the cause of death.

However, the mechanism of the fatal and the nonfatal immediate reactions are probably basically similar, and differ only in degree.

Hyman[8] suggested that fatal reactions to mercupurin are nonspecific, and produce incoagulability of the blood, as does "speed shock," which may occur when any material is rapidly injected intravenously. The symptomatology of "speed shock," as described by Hirshfeld, et al.,[9, 10] is variable, but, generally within one minute after a rapid intravenous injection, salivation, vomiting, diarrhea, dyspnea, often with irregular respiration, muscle atony or muscle spasm, a fall in blood pressure, and bronchospasm may occur. There is no constancy about the appearance of any of these symptoms in experimental animals. It is stated that, when "speed shock" does occur, the blood is rendered incoagulable. However, the blood of one of our patients, taken about five minutes after death, clotted firmly and promptly, but did undergo apparently complete fibrinolysis about fifteen to thirty minutes later. According to the work of Skundina,[11] this spontaneous fibrinolysis is not specific for "speed shock" or mercurial intoxication, but is usually found in patients who die suddenly with severe shock from any cause.

Jackson[12] produced ventricular fibrillation and death in dogs within three to five minutes after the intravenous injection of 5 c.c. of a 2 per

cent solution of salyrgan. If both vagi were cut prior to the injection, death resulted from respiratory paralysis without ventricular fibrillation. Chastain and Mackie,[13] Barker, et al.,[7] DeGraff and Lehman,[14] and others, employing various mercurial injections in experimental animals, noted no difference after vagotomy, but otherwise obtained similar results. Whether the same mechanism pertains to man awaits further investigation. Clinical observations suggest that the mechanism is the same, at least in so far as the fact that the heart seems primarily involved. Essentially the same clinical picture is seen when cardiac patients die suddenly. We have watched two patients with myocardial infarcts die of ventricular fibrillation while an electrocardiographic recording was being made. These patients presented a picture that was almost identical to what has been described above, consisting of marked cyanosis, absence of the radial pulse and blood pressure, and whirring precordial noise without recognizable heart sounds. Gasping respirations continued for two to three minutes.

It has been suggested in the earlier reports that the reactions are anaphylactic in nature. There seems to be adequate evidence against this explanation of the type of reaction under discussion. First of all, the collapse which has been observed in all fatal reactions and in some of the nonfatal reactions has always been "cardiac collapse," i.e., acute forward failure, and not the peripheral vascular collapse which generally accompanies anaphylactic reactions. All of the *immediate* fatal and nonfatal reactions have occurred after *intravenous* injection of a mercurial.* In cases of nonfatal immediate reactions, subsequent intramuscular injections have caused no reaction.[6] On the other hand, patients who have shown definite allergic reactions, such as urticaria, rash, fever, etc., after intravenous injection of mercurials, showed the same reactions when the mercurial was administered intramuscularly, or in the form of a rectal suppository.[15, 16, 18] The fact that the early fatalities which were reported occurred after multiple, apparently asymptomatic injections outwardly seemed to favor anaphylaxis; the reasoning was that the preliminary injections sensitized the patient, thus setting the stage for the fatal reaction. However, at least three cases appear in the literature in which death followed the first injection.[2, 7, 19]

The suggestion that the mechanism is simply a toxic reaction to the mercury ion seems fairly well supported by laboratory and clinical observations. Salant and Kleitman,[20] in perfusion experiments with inorganic mercury salts, have produced marked disturbances in the rhythm of the turtle heart. They found that the time required to obtain toxic effects on the heart varied with the concentration of the mercury salt. "Delirium cordis" was produced with dilutions as high

*We have omitted from this review deaths reported after the use of older mercury preparations which caused symptoms typical of mercury poisoning because these were not immediate sudden deaths, and represent an entirely different syndrome. The case reported by Molnár,[17] in which death followed twenty to twenty-five minutes after the intraperitoneal injection of 2 c.c. of mercury, likewise does not come under the syndrome of sudden immediate death.

as 1:10,000,000. Similar results were obtained with the acetate, succinate, and benzoate of mercury, thus excluding the role of the anion. Their results with cats and dogs were similar to those of more recent studies on the toxicity of the organic mercurials,[7, 12-14] although they do not mention ventricular fibrillation, but speak of "delirium cordis."

Sollmann[21] states that mercury is rapidly removed from the blood stream, and stored especially in the kidneys and liver. From these depots traces of mercury may be mobilized for as long as six months. The chief channels for the excretion of mercury are the kidneys and the gastrointestinal tract. After a single dose, excretion begins within a few hours and may last for as long as eight days. After a series of injections, excretion of small amounts may persist intermittently for several months. Goodman and Gilman[22] essentially agree with this. DeGraff, et al.,[23] studying the effect of theophylline on the excretion of mercury in rabbits, showed that nearly 100 per cent of the mercury was excreted at the end of six hours. The preparations used were mercurin and salyrgan with and without theophylline, and the dose was 3.71 mg. of mercury in the salyrgan experiments and 3.8 mg. of mercury in the mercurin experiments. The possibility of cumulation in patients with impaired renal function, and, perhaps to less extent, in patients with prolonged circulation time, is not excluded, and may possibly account for the greater frequency of fatal reactions after multiple injections.

In summary, it may be said that toxic effects on the heart are possible with very low concentrations of mercury in the blood if these concentrations are maintained for a sufficiently long period of time. Cardiac failure and impaired renal function favor a higher concentration of mercury and tend to maintain that concentration for a longer period of time. The possible cumulation of mercury in the presence of cardiorenal disease may account for the greater incidence of serious reactions after multiple injections of mercurials.

Delayed Reactions.—The nonfatal delayed reactions may well be incidental to the physiologic effects consequent on the diuretic action of the drug. Swigert and Fitz[24] have shown that, in some patients, a transitory increase in plasma volume occurs after salyrgan is given; and Calvin, Decherd, and Herrmann[25] have also made this observation in two cases in which diuresis was delayed or failed to occur. This can account for pulmonary edema or bronchial congestion, with asthmatic type of respiration, in patients with little cardiac reserve. It is not unlikely that, in those who develop asthma, the cardiovascular disturbance is essentially the same as in the patients who develop pulmonary edema, for it is well known that, in paroxysmal nocturnal dyspnea, asthmatic breathing either may be absent or may dominate the picture. The occurrence of pulmonary edema after intravenous mercurial diuretic administration has been noted by several observers.[15, 24, 26]

In two of our patients, cyanosis and dyspnea followed a chill. In these cases the possibility exists that the chill was a nonspecific reaction, such as is occasionally seen after any type of intravenous therapy, and that this, in turn, so disturbed the cardiovascular system that pulmonary edema resulted. There is, however, evidence[1, 18, 26] that repeated chills may be specific reactions, for, in some cases, chills have recurred regularly after each injection of a mercurial diuretic.

In discussing this group, it is appropriate to mention the occasional case of mild digitalis intoxication which occurs in digitalized patients after marked diuresis. In our experience the symptoms have not been very troublesome, and have generally disappeared completely within twenty-four hours. Such cases are not common; more often, the accentuation of the digitalis effect may be manifested by slowing of the heart rate after a good diuretic response to the drug.

In our experience, elevation of blood nonprotein nitrogen after mercurial diuretics is rare, but does occur. The explanation of these rare elevations in nonprotein nitrogen is more likely to be found in the loss of electrolytes and water, resulting in dehydration, rather than in a nephrotoxic action of the mercury. Similar complications resulting from the pharmacologic action of mercurial diuretics are fully discussed by DeGraff and Nadler.[15]

PREVENTION OF REACTIONS

At present there is no known method of preventing fatal reactions. However, the following points are worth bearing in mind.

1. The incidence of fatal reactions is quite low. In this hospital, during a sixteen-month period, about 5,200 ampoules of mercupurin were issued, and, during this approximate period, two known fatalities occurred.

The incidence of nonfatal reactions is greater, for we have noted, during this same period, at least nine; five were of the immediate type and of sufficient severity to cause alarm to both the patient and the physician; and mild immediate reactions have occurred not uncommonly.

2. Most of the fatal reactions are preceded by nonfatal reactions which, if of the more serious immediate type, should serve as a warning, and, thereafter, mercurials should not be given except when other measures have failed, and then only with great caution; if feasible, they should be administered intramuscularly or in suppository form. Only three fatalities have been reported after the first injection of a mercurial diuretic. There is no evidence that dilution of the drug in 10 c.c. of water or normal saline protects against reactions, for these have been observed when such dilute solutions have been used,[19] and the experimental work of DeGraff, et al.,[14] offers evidence against any rationale for such dilution.

3. There is no indication that changing from one preparation to another is a safeguard against *fatal* reactions. However, nonfatal delayed

reactions may in some cases be specific for a given preparation. Thus, in the case reported by Fox, Gold, and Leon,[18] serious reactions, consisting of fever, erythema, paresthesias, and, occasionally, ulcerative stomatitis, followed the use of mercupurin intravenously or a mercurin suppository, but only very mild reactions occurred after salyrgan and inorganic mercurials.

4. Our experience here, and the experience of others as expressed in the literature, would indicate that the common drugs prescribed in heart failure, such as digitalis, ammonium chloride, nitrites, aminophylline, etc., have no effect on the toxicity of mercurial diuretics, nor does the type of heart or renal disease. Patients who are already very ill are perhaps more likely to succumb than those in a better state of health, for they are less able to stand the strain of a reaction. A relatively good state of health is, however, no protection against a fatal reaction, as is evident in our second case.

SUMMARY

Two fatal reactions to the intravenous administration of mercupurin, with post-mortem observations, are reported. Various nonfatal reactions to mercupurin are described and divided into the immediate and delayed types. The relation of the immediate type of nonfatal reaction to fatal reactions is stressed. The mechanism of the reactions to mercurial diuretics is discussed, and it is concluded that the fatal and the immediate nonfatal reactions probably result from a direct toxic effect of mercury on the heart, whereas the delayed nonfatal reactions are incidental to the diuretic action of the drug. These conclusions seem to be substantiated by experimental work on animals, as reported in the literature, and by our own clinical observations. At present there is no known way of preventing fatal reactions.

Since mercurial diuretic drugs are valuable therapeutic agents in the treatment of congestive heart failure, and since the frequency of severe or fatal reactions to their administration is low, the usefulness of these drugs outweighs their possible danger. They should, however, be administered only when clearly indicated, and the occurrence of danger signals, which have been discussed, warrants a complete reevaluation of the therapeutic regimen in any given case. It is well to remember that, at the present time, no fatalities have been reported after intramuscular injection of a mercurial diuretic, and that the diuretic response often compares favorably with that which results from intravenous injection.

REFERENCES

1. Wolf, I. J., and Bongiorno, H. C.: Sudden Death With Salyrgan, Canad. M. A. J. 25: 73, 1931.
2. Cadbury, W. W.: Idiosyncrasy to Salyrgan, Medical Papers Dedicated to H. A. Christian, Baltimore, 1936, The Waverly Press, pp. 259-260.
3. Greenwold, H. M., and Jacobson, S.: Sudden Death Due to Mercurial Diuretics, J. Pediat. 11: 540, 1937.

4. Tyson, Mary C.: Danger of Intravenous Mercurial Injections in Nephrosis, J. A. M. A. **117**: 998, 1941.
5. Friedfeld, L., Kissin, M., Modell, W., and Sussman, R.: Communication on Mercupurin, J. A. M. A. **117**: 1806, 1941.
6. Brown, G., Friedfeld, R., Kissin, M., Modell, W., and Sussman, R. M.: Deaths Immediately Following the Intravenous Administration of Mercupurin, J. A. M. A. **119**: 1004, 1942.
7. Barker, M. M., Lindberg, H. A., and Thomas, M. E.: Sudden Death and Mercurial Diuretics, J. A. M. A. **119**: 1001, 1942.
8. Hyman, H. T.: Sudden Death After Use of Mercurial Diuretics, Communication, J. A. M. A. **119**: 1444, 1942.
9. Hirshfeld, S., Hyman, H. T., and Wanger, J. J.: Influence of Velocity on the Response to Intravenous Injections, Arch. Int. Med. **47**: 259, 1931.
10. Hirshfeld, S., Hyman, H. T., and Wanger, J. J.: Studies of Velocity and the Response to Intravenous Injections, J. A. M. A. **96**: 1221, 1931.
11. Riddell, V. H.: Blood Transfusion, New York and London, 1939, Oxford University Press, pp. 313-316.
12. Jackson, D. E.: Action of Mercury in Organic Combination, J. Pharmacol. & Exper. Therap. **29**: 471, 1926.
13. Chastain, L. L., and Mackie, G. C.: Studies on Toxicity of New Mercurial Diuretic (Sodium Salt of Pyridine-dicarboxy-mercuri-hydroxyl-propyl-amide-theophyllin), South. Med. & Surg. **102**: 5, 1940.
14. DeGraff, A. C., and Lehman, R. A.: The Acute Toxicity of Mercurial Diuretics, J. A. M. A. **119**: 998, 1942.
15. DeGraff, A. C., and Nadler, J. E.: A Review of Toxic Manifestations of Mercurial Diuretics in Man, J. A. M. A. **119**: 1006, 1942.
16. Kling, E. M., and Seymour, W. B.: Systemic Reactions to Mercurial Diuretics, Am. J. M. Sc. **203**: 874, 1942.
17. Molnár, I.: Plötzlicher Tod nach einer intraperitonealen Novurit-Injektion, Klin. Wchnschr. **14**: 239, 1935.
18. Fox, T. T., Gold, H., and Leon, J.: Hypersensitiveness to a Mercurial Diuretic, J. A. M. A. **119**: 1497, 1942.
19. Sundaram, S. K.: Idiosyncrasy to Salyrgan, Communication, J. A. M. A. **103**: 60, 1934.
20. Salant, W., and Kleitman, N.: Observations on the Action of Mercury, J. Pharmacol. & Exper. Therap. **19**: 315, 1922.
21. Sollmann, T.: A Manual of Pharmacology, Philadelphia, 1936, W. B. Saunders Co., pp. 1031-1033.
22. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, 1941, The Macmillan Co., pp. 642, 732.
23. DeGraff, A. C., Batterman, R. C., Lehman, R. A., and Yasuna, E.: Excretion of Mercury Following Administration of Mercurial Diuretics With and Without Theophylline, Proc. Soc. Exper. Biol. & Med. **39**: 250, 1938.
24. Swigert, N. W., and Fitz, R.: The Effect of Mersalyl (Salyrgan) on Plasma Volume, J. A. M. A. **115**: 1786, 1940.
25. Calvin, D. B., Decherd, G., and Herrmann, G.: Response of Plasma Volume to Diuretics, Proc. Soc. Exper. Biol. & Med. **44**: 529, 1940.
26. Higgins, W. H.: Acute Toxic Effects of Mercurial Diuretics, J. A. M. A. **119**: 1182, 1942.

EXPERIMENTS WITH CALCULATED THERAPEUTIC AND TOXIC DOSES OF DIGITALIS

V. Comparative Effects of Toxic Doses of Digitalis and of Pitressin on the Electrocardiogram, Heart, and Brain*

William H. Dearing, M.D.,† Arlie R. Barnes, M.D.,† and Hiram E. Essex, Ph.D.‡
Rochester, Minn.

THE purpose of these studies was to ascertain whether repeated, large doses of the vasoconstrictor, pitressin, could induce changes in the electrocardiogram, in the myocardium, and in the brain which resembled those produced by toxic doses of digitalis.

LITERATURE

Various cardiovascular responses to posterior pituitary extracts have been studied since 1895, when Oliver and Schäfer[1] showed that their extracts were capable of producing a rise of the blood pressure and a slowing of the heart rate. Howell[2] and von Cyon[3] observed similar changes after posterior pituitary extracts had been administered to dogs and rabbits. Szymonowicz[4] described a slight decrease of the blood pressure and rise of the cardiac rate. Schäfer and Vincent[5] stated that pressor and depressor substances existed in their extracts. The pressor effect was accompanied by slowing of the heart rate. Garnier and Thaon[6] described a brief rise, then a fall, and, finally, a substantial rise of the arterial pressure of the rabbit after posterior pituitary extracts had been administered. Paukow[7] and Fühner[8] observed changes in blood pressure similar to those noted by Garnier and Thaon. Gruber[9] reported that vasopressin produced a rise of the blood pressure in all doses when injected intravenously into dogs anesthetized with chloretone; a fall of blood pressure occurred in unanesthetized dogs. Gruber and Kountz[10] stated that pitressin caused, first, a decrease of the heart rate during the primary rise of blood pressure, and then an acceleration of the heart rate during the fall in blood pressure; finally, the cardiac rate decreased during the prolonged rise of blood pressure. Goldenberg and Rothberger[11] observed a decrease of the blood pressure after the administration of pitressin to dogs. They considered that this reaction was the result of diminished cardiac output produced by the effects of coronary spasm on the myocardium.

Isolated arterial rings immersed in pituitary extracts were found to be decreased in caliber by de Bonis and Susanna[12] and by Pal.[13] On

Received for publication Feb. 28, 1943.

*Abridgment of portion of thesis submitted by Dr. Dearing to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Ph.D. in Medicine.

†Division of Medicine, Mayo Clinic.
‡Division of Experimental Medicine, Mayo Foundation.

the contrary, Cow[14] stated that rings of coronary arteries were sometimes constricted and sometimes dilated. Rischbieter[15] observed that the ear vessels of the rabbit constricted after the administration of pituitary extracts. Geiling, Herrick, and Essex[16] found that pressor fractions from the posterior lobe of the pituitary gland reduced the blood flow in the femoral artery and vein. They used the thermostromuhr to measure the volume of blood flow.

The effects of extracts of the posterior lobe of the pituitary on the coronary blood flow in isolated heart preparations have been studied by numerous investigators. Dale[17] found a diminution of the coronary blood flow, along with a decrease of the strength of cardiac contraction. Meyer[18] did not observe any significant change in the coronary blood flow. Rabe[19] reported that either a contraction or a dilatation occurred. Gunn[20] described a diminution of 70 per cent in the coronary blood flow. Gruber[21] stated that neutralized pituitary extracts caused coronary vasoconstriction, but that unneutralized commercial extracts caused vasodilatation. Gruber and Kountz[22] observed that pitressin in both alkaline and acid solutions produced vasoconstriction of the coronary vessels.

Morawitz and Zahn,[23] Bodo,[24] Rössler,[25] and Ross, Dreyer, and Stehle[26] stated that the coronary blood flow, as measured by the Morawitz cannula method, is diminished by posterior pituitary preparations.

Anrep and Stacey[27] and Häusler[28] showed that posterior pituitary extracts decrease the coronary blood flow as measured by the hot-wire anemometer.

The thermostromuhr has been used in recent years to measure the coronary blood flow after the administration of pitressin. Hochrein[29] observed an increase of the coronary blood flow, whereas Dietrich[30] and Essex, Wegria, Herrick, and Mann[31] described marked decreases. The latter authors showed that the blood flow may remain less than the control level as long as forty-five minutes.

Numerous electrocardiographic changes after the administration of posterior pituitary extracts have been described by Claude, Porak, and Routier,[32, 33] Hecht and Nadel,[34] Resnik and Geiling,[35] Gruber and Kountz,[36] Goldenberg and Rothberger,[11] and Dietrich.[30]

METHODS

These experiments were done on fifteen trained cats.

The pitressin (20 pressor units per cubic centimeter) was prepared by Parke, Davis and Company. Usually the extract was administered intravenously; occasionally the intramuscular route was used.

Electrocardiograms were made on each animal.[37] The tracings were made before the pitressin was injected and at various intervals after its administration. In some animals the tracings were made during the injection and at intervals of only a few seconds; in others the tracings were made every five minutes, ten minutes, or fifteen minutes. In the more prolonged experiments, electrocardiograms were taken hourly or daily.

TABLE I

CORRELATION OF THE DOSAGE OF PITRESSIN, THE TIME INTERVALS, AND THE HISTOLOGIC STUDIES OF THE MYOCARDIUM

DATE	TIME	DOSAGE OF PITRESSIN (C.C.)	MODE OF ADMINISTRATION	DURATION OF EXPERIMENT	HISTOLOGIC CHANGES				
					PAPILLARY MUSCLE AND LEFT VENTRICLE	INTERVENTRICULAR SEPTUM	RIGHT VENTRICLE	LEFT ATRIUM	RIGHT ATRIUM
5/ 3/38	9:00 A.M.	3	Intravenous	Died on 2nd day	Yes +++	Yes ++	Yes +	No	No
	2:00 P.M.	3	Intravenous						
5/18/38	8:20 P.M.	3	Intravenous	Died on 2nd day	Yes ++	Yes +±	Yes +	Yes ±	±?
	10:45 A.M.	3	Intravenous						
	1:45 P.M.	3	Intravenous						
	4:30 P.M.	2	Intravenous						
5/10/38	9:15 A.M.	3	Intravenous	Died late on 2nd day	Yes ++	Yes ++	Yes ±	No	No
	11:40 A.M.	2	Intravenous						
	1:30 P.M.	2	Intravenous						
	3:35 P.M.	3	Intravenous						
5/11/38	8:40 A.M.	3	Intravenous						
5/24/38	8:10 A.M.	3	Intravenous	Died on 3rd day	Yes ++	Yes +	No	No	No
	10:40 A.M.	3	Intravenous						
	2:20 P.M.	2	Intravenous						
5/25/38	8:15 A.M.	2	Intravenous						
	3:30 P.M.	2	Intravenous						
5/30/38	8:15 A.M.	3	Intravenous	Died on 4th day	Yes ++	Yes ++	No	No	No
	10:30 A.M.	3	Intravenous						
	3:20 P.M.	2	Intravenous						
5/31/38	10:15 A.M.	2	Intravenous						
5/11/38	9:40 A.M.	1.8	Intravenous	Died on 13th day	Yes ++++	Yes +++	Yes ++	±?	+
	11:45 A.M.	2	Intravenous						
	1:45 P.M.	3	Intravenous						
	2:15 P.M.	2	Intramuscular						
	4:00 P.M.	1.6	Intramuscular						
5/12/38	8:50 A.M.	3	Intravenous						
	11:15 A.M.	2.6	Intravenous						
	1:50 P.M.	3	Intravenous						
5/13/38	9:00 A.M.	3	Intravenous						
	11:00 A.M.	3	Intravenous						
5/18/38	12:00 M.	3	Intravenous						
6/27/38	8:10 A.M.	3	Intravenous	Killed on 5th day	No	No	No	No	No
	12:00 M.	2	Intravenous						
6/28/38	8:00 A.M.	2	Intravenous						
6/29/38	8:00 A.M.	3	Intravenous						
6/30/38	8:00 A.M.	2	Intravenous						
5/ 2/38	8:50 A.M.	2	Intravenous	Died on 5th day	No	No	No	No	No
	10:50 A.M.	2	Intramuscular						
	11:50 A.M.	2	Intramuscular						
	1:50 P.M.	1.6	Intravenous						
	4:30 P.M.	2	Intravenous						
5/ 3/38	8:50 A.M.	2	Intravenous						
	11:50 A.M.	2	Intravenous						
	1:45 P.M.	2	Intravenous						
	2:30 P.M.	2	Intramuscular						
	4:45 P.M.	2	Intravenous						
5/ 4/38	9:45 A.M.	2	Intravenous						
	2:15 P.M.	2	Intravenous						
	4:50 P.M.	2	Intravenous						
5/ 5/38	9:00 A.M.	3	Intramuscular						
	11:00 A.M.	2	Intramuscular						
	1:45 P.M.	2	Intramuscular						
	3:45 P.M.	2	Intramuscular						
	4:50 P.M.	2	Intramuscular						

TABLE 1—CONT'D

DATE	TIME	DOSAGE OF PITRESSIN (C.C.)	MODE OF ADMINISTRATION	DURATION OF EXPERIMENT	HISTOLOGIC CHANGES				
					PAPILLARY MUSCLE AND LEFT VENTRICLE	INTERVENTRICULAR SEPTUM	RIGHT VENTRICLE	LEFT ATRIUM	RIGHT ATRIUM
4/25/38	8:30 A.M.	2	Intravenous	Killed on 8th day	No	No	No	No	No
	10:30 A.M.	2	Intravenous						
	2:30 P.M.	2	Intravenous						
	4:50 P.M.	2	Intravenous						
4/26/38	9:00 A.M.	2	Intravenous						
	1:45 P.M.	3	Intramuscular						
4/27/38	9:00 A.M.	2	Intramuscular						
	11:00 A.M.	2	Intramuscular						
	1:45 P.M.	3	Intramuscular						
	4:00 P.M.	3	Intramuscular						
4/28/38	8:30 A.M.	2	Intramuscular						
	10:30 A.M.	2	Intramuscular						
	12:30 P.M.	2	Intramuscular						
	2:30 P.M.	2	Intramuscular						
	4:30 P.M.	2	Intramuscular						
4/29/38	8:25 A.M.	2	Intravenous						
	10:30 A.M.	2	Intravenous						
	12:30 P.M.	2	Intramuscular						
4/30/38	8:00 A.M.	3	Intravenous						
6/19/38	8:00 A.M.	3	Intravenous	Killed on 10th day	±	±	No	No	No
6/20/38	8:00 A.M.	3	Intramuscular						
6/21/38	8:00 A.M.	3	Intramuscular						
6/23/38	8:00 A.M.	3	Intravenous						
6/13/38	10:00 A.M.	2.8	Intravenous	Killed on 16th day	No	No	No	No	No
	2:45 P.M.	3	Intravenous						
6/14/38	2:30 P.M.	2	Intravenous						
6/17/38	1:58 P.M.	1.5	Intravenous						
6/18/38	10:00 A.M.	2	Intramuscular						
6/20/38	8:00 A.M.	2	Intramuscular						
6/21/38	8:00 A.M.	2	Intramuscular						
6/22/38	11:00 A.M.	3	Intramuscular						
6/24/38	8:00 A.M.	3	Intramuscular						
6/25/38	9:40 A.M.	3	Intramuscular						
6/27/38	8:00 A.M.	2	Intramuscular						
6/19/38	10:20 A.M.	3	Intravenous	Killed on 10th day	No	No	No	No	No
	4:00 P.M.	3	Intravenous						
6/19/38	11:00 A.M.	0.1	Intravenous	Killed on 12th day	No	No	No	No	No
	1:30 P.M.	0.1	Intravenous						
	3:30 P.M.	0.1	Intravenous						
6/20/38	As on 6/19/38								
6/21/38	As on 6/19/38								
6/22/38	As on 6/19/38								
6/23/38	As on 6/19/38								
6/28/38	8:00 A.M.	3	Intravenous						
5/19/38	8:25 A.M.	3	Intravenous	Killed on 33rd day	No	No	No	No	No
	10:25 A.M.	3	Intravenous						
	12:10 P.M.	2	Intravenous						
	2:40 P.M.	2	Intravenous						
	4:30 P.M.	2	Intramuscular						
5/20/38	9:00 A.M.	3	Intravenous						
	2:20 P.M.	3	Intravenous						
5/23/38	9:15 A.M.	3	Intravenous						
	2:50 P.M.	3	Intravenous						
	4:30 P.M.	2	Intramuscular						
5/24/38	11:30 A.M.	3	Intramuscular						
	3:50 P.M.	2	Intravenous						
5/26/38	3:00 P.M.	3	Intramuscular						

TABLE I—CONT'D

DATE	TIME	DOSAGE OF PITRESSIN (C.C.)	MODE OF ADMINISTRATION	DURATION OF EXPERIMENT	HISTOLOGIC CHANGES				
					PAPILLARY MUSCLE AND LEFT VENTRICLE	INTERVENTRICULAR SEPTUM	RIGHT VENTRICLE	LEFT ATRIUM	RIGHT ATRIUM
4/ 5/38	8:50 A.M.	0.3	Intravenous	Killed on 10th day	No	No	No	No	No
	10:50 A.M.	0.3	Intravenous						
	12:50 P.M.	0.5	Intravenous						
	2:50 P.M.	0.6	Intravenous						
	4:50 P.M.	0.75	Intravenous						
4/ 6/38	8:10 A.M.	0.5	Intravenous						
	10:10 A.M.	0.75	Intravenous						
	12:10 P.M.	0.1	Intravenous						
	2:40 P.M.	1	Intramuscular						
	4:40 P.M.	1	Intravenous						
4/ 7/38	8:40 A.M.	1	Intravenous						
	10:40 A.M.	1	Intravenous						
	12:50 P.M.	1	Intramuscular						
	3:15 P.M.	1	Intramuscular						
4/ 8/38	8:30 A.M.	1	Intravenous						
	10:30 A.M.	1	Intravenous						
	3:20 P.M.	1	Intravenous						
4/12/38	8:50 A.M.	2	Intramuscular						
	2:00 P.M.	2	Intramuscular						

Notes were compiled on the reaction of each animal to every injection of pitressin.

Those animals which did not die spontaneously were killed, after various periods, in an ether or chloroform chamber. Necropsies were performed immediately. The brain, spinal cord, heart, stomach, duodenum, ileum, uterus, diaphragm, biceps, and musculature of the abdominal wall were prepared for microscopic study as described in a previous paper.[38]

The animals described in a previous paper[38] served as controls.

RESULTS

A. Anatomic Studies of the Myocardium After Repeated Injection of Large Doses of Pitressin.—Fifteen cats were used in these experiments on the effect of repeated, large doses of pitressin on the structure of the myocardium.

Anatomic changes were observed in the cardiac muscle of six of the fifteen animals. Table I illustrates the number of doses of pitressin, the size of each dose, the mode of administration of the preparation, the duration of the experiment from the first injection of pitressin to the death of the animal, and the result of the histologic study of the myocardium.

The myocardial lesions resembled those seen after toxic doses of digitalis had been given, although the lesions produced by digitalis tended to be more extensive than those produced by pitressin. The anatomic changes in the myocardium were focal in distribution, as we noted with the lesions produced by digitalis. The early, definite changes

consisted of degeneration of the myocardial fibers (Fig. 1). Hemorrhage was commonly found in the early myocardial lesions. Later, exudative cells entered the zone of myocardial degeneration. The histologic changes were most likely to be found in the papillary muscle and in the region just beneath the endocardium of the left ventricle.

No evidence of arteriosclerosis was seen in any of the cardiac arteries or arterioles. Small, macroscopic, reddish verrucae were noted on the mitral valves in some of the animals. Subendocardial hemorrhages were observed macroscopically in several animals. Small doses of pitressin did not produce demonstrable histologic damage in the myocardium.

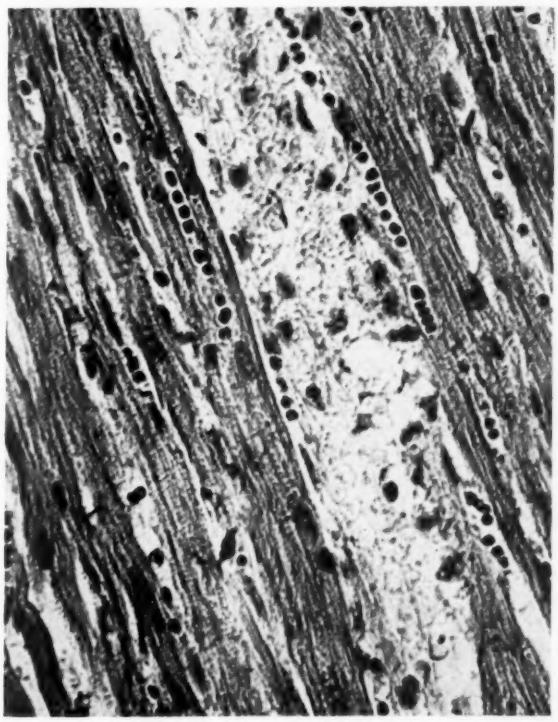

Fig. 1.—Degenerative changes in myocardial fibers after repeated injection of large doses of pitressin (×450).

The observation, made by many previous investigators, that second doses of pitressin may not produce any significant cardiovascular reaction, was confirmed. The fact that second doses of pitressin, injected too soon after the first dose, may not cause a significant decrease of the coronary flow may account for some, but perhaps not all, of our failures to bring about myocardial lesions in a number of animals.

The old animals were the only ones in which myocardial lesions developed. Myocardial changes were not found in several young cats.

B. Electrocardiographic Studies During the Repeated Administration of Large Doses of Pitressin.—The changes of the RS-T segment and T

wave which occurred during and after the administration of repeated doses of pitressin were as follows: (1) decrease of the height of the T wave in one or more leads; (2) increase of the height of the T wave in one or more leads; (3) simple inversion of the T wave in one or more leads; (4) depression of the RS-T segment in one or more leads; (5) elevation of the RS-T segment in one or more leads (not of the plateau type); (6) cove-plane, negative T_2 and T_3, associated with a positive T_1; (7) negative T_1 and T_2, associated with a positive T_3.

All the animals at one time or another showed changes in the height of the T waves or simple inversion of the T wave in one or more leads. Elevation of the RS-T segment (similar to that shown in Fig. 1*d* of the second paper in this series)[37] frequently was seen immediately after the pitressin had been injected; this elevation, however, did not persist long. The plateau type of elevation of the RS-T segment which occurred after administration of toxic doses of digitalis was not observed in the animals which received pitressin.

Depression of the RS-T segment (Fig. 2) was observed in a number of the animals. This pattern was striking in four cats.

The cove-plane, negative T_2 and T_3 pattern (Fig. 3) was found in two cats; both of these animals had degenerative lesions in the myocardium. One cat in which myocardial lesions developed did not show any significant changes in the RS-T segment or T wave in any of the electrocardiograms which were made each day.

Numerous other electrocardiographic changes were noted: profound sinus bradycardia, sinus tachycardia, bigeminy, ventricular premature contractions, complete heart block, ventricular tachycardia, and ventricular fibrillation. These changes after the administration of pitressin have been described by numerous previous investigators and do not need to be elaborated on.

TABLE II

CORRELATION OF THE DOSAGE OF PITRESSIN, THE TIME INTERVAL, AND THE HISTOLOGIC STUDIES ON THE CENTRAL NERVOUS SYSTEM*

DURATION OF EXPERIMENT	HISTOLOGIC CHANGES			
	CEREBRUM	CEREBELLUM	PONS	SPINAL CORD
Died on 2nd day	–	–	–	–
Died on 2nd day	–	–	–	–
Died late on 2nd day	Yes ++	No	Yes ±	No
Died on 3rd day	–	–	–	–
Died on 4th day	Yes ++	Yes +	Yes ±	No
Died on 13th day	–	–	–	–
Killed on 5th day	No	No	No	No
Died on 5th day	No	No	No	No
Killed on 8th day	No	No	No	No
Killed on 10th day	–	–	–	–
Killed on 16th day	No	No	No	No
Killed on 10th day	No	No	No	No
Killed on 12th day	No	No	No	No
Killed on 33rd day	No	No	No	No
Killed on 10th day	No	No	No	No

*For date, time, dose, and mode of administration, see Table I.

C. Anatomic Studies of the Central Nervous System After Repeated Injection of Large Doses of Pitressin.—Two of the six animals in which myocardial lesions were found after repeated injection of large doses of pitressin were suitable for microscopic examination of the brain. The

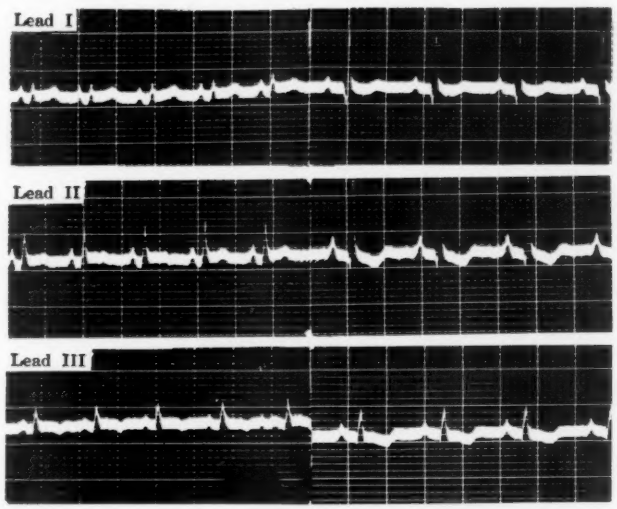

Fig. 2.—On the left, control electrocardiogram; on the right, depression of the RS-T segments after repeated injection of large doses of pitressin.

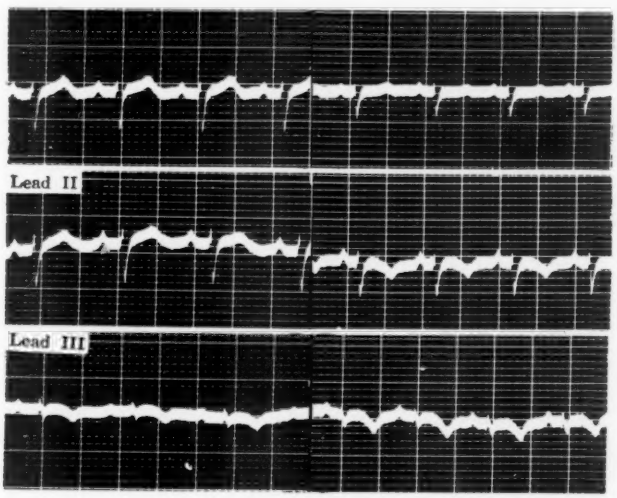

Fig. 3.—On the left, control electrocardiogram; on the right, cove-plane, negative T_2 and T_3 after repeated injection of large doses of pitressin.

brain and spinal cord of these two animals were removed immediately after spontaneous death. Table II illustrates the distribution of the lesions. The cerebral cortex was the most vulnerable. No changes were found in the cells of the spinal cord.

The brain and spinal cord of the remaining eights animals (Table II) were free from evidence of significant cellular lesions.

Fig. 4 illustrates the degeneration which was seen in the pyramidal cells of the cerebral cortex after repeated injection of doses of pitressin. The cortical cells after the administration of pitressin showed swelling, vacuolization, degeneration (necrosis), and pyknosis. These cellular changes resembled those that occurred after the administration of toxic doses of digitalis. However, the cortical lesions were much less extensive than some of those which were observed after toxic doses of digitalis had been administered.

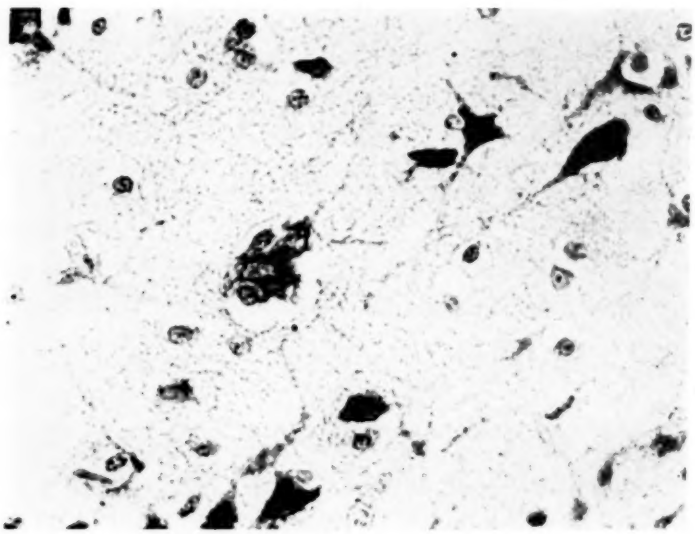

Fig. 4.—Degenerative changes in pyramidal cells of the cerebral cortex after repeated injection of large doses of pitressin (×450).

D. Macroscopic and Microscopic Changes in the Stomach After Repeated Injection of Large Doses of Pitressin.—These observations are confirmatory of those reported by Dodds, Noble, and Smith[39] and Dodds, Noble, Scarff, and Williams.[40]

In our studies, changes in the stomach were produced by repeated, large doses of pitressin. Macroscopically, the gastric mucosa of the fundus and upper portion of the pylorus was eroded by numerous ulcers. The mucous membrane of the stomach was either red from hemorrhage or black from the action of acid on the extravascular hemoglobin.

Microscopically, the mucosa of the stomach showed varying degrees of degeneration of the fundic cells. Hemorrhage was a prominent feature in these lesions. The gastric smooth muscle was unchanged in the animals studied in our experiment.

The mucosa of the duodenum was entirely normal, both macroscopically and microscopically, even when the gastric lesions were extensive.

E. Signs Observed in the Cats After Injection of Large Doses of Pitressin.—An initial intravenous dose of 3 c.c. of pitressin caused profound bradycardia and, frequently, brief respiratory arrest. Paling of the oral mucosa, panting respirations, and ataxia soon appeared. Vomiting, urination, and defecation often occurred. These effects have been described by many previous workers. Recovery of the animal was gradual.

A second dose of pitressin, given soon after the initial dose, did not produce those changes, or, if they did occur, they were mild.

When the doses of pitressin were properly spaced, there was a recurrence of the foregoing effects each time the extract was administered intravenously.

After two or three doses of pitressin had been injected on the first day, the animals became very hungry and consumed large quantities of meat. A mucoid, diarrheal discharge often appeared at the end of the first day of treatment with one, two, or three large doses of pitressin.

Small doses of pitressin (0.1 c.c.) produced little external change in the animal. Bradycardia could be detected by palpation of the heartbeat or by the electrocardiogram.

The older the animal, the more striking were the untoward physical signs after the injection of a large dose of pitressin. Young animals tolerate large doses of pitressin better than the old ones.

COMMENT

The myocardial lesions are not easy to produce with repeated doses of pitressin. The dose of pitressin must be large, the time interval between succeeding injections must be optimal, and the animal must be old.

Doses of pitressin which are administered too soon after the initial injection are likely to produce little measurable change in the cardiovascular system. The coronary blood flow, in particular, may not be decreased by these repeated injections of pitressin, a fact known to Dale[17] in his early experiments with pituitary extracts. Furthermore, the decrease of coronary blood flow after administration of pitressin, although pronounced, is not sustained for a period longer than forty-five minutes (Essex, Wegria, Herrick, and Mann[31]). Therefore, if our assumption is correct, that the myocardial lesions in our experiment on the effect of pitressin are related to the decrease of the coronary blood flow, the experimental conditions must be optimal in order to attain repeated, sustained diminutions of the coronary blood flow.

We wish to avoid an error in the interpretation of our experiments by stating that it does not necessarily follow that the myocardial lesions produced by digitalis are induced by vasoconstriction in the coronary arteries just because pitressin decreased the coronary blood flow and

produced myocardial lesions which resemble those seen after the administration of toxic doses of digitalis.

SUMMARY

Histologic changes were observed in the myocardium after the repeated injection of large doses of pitressin. The myocardial lesions resembled those which occurred after the administration of toxic doses of digitalis. They were focal in distribution and were most prominent in the subendocardial layer of the left ventricular musculature.

The following is a summary of the changes in the RS-T segment and T wave after large doses of pitressin: (1) decrease or increase of the height of the T wave; (2) elevation of the RS-T segment (not of the plateau type) in one or more leads; (3) simple inversion of the T wave in one or more leads; (4) depression of the RS-T segment in one or more leads; (5) cove-plane, negative T_2 and T_3; and (6) cove-plane, negative T_1 and T_2.

Cellular degeneration was observed in the cerebral cortex after the repeated injection of large doses of pitressin.

Myocardial and cerebral lesions were not observed in all the animals which received large doses of pitressin.

Myocardial lesions were produced in the older, but not the younger, animals.

Gastric lesions were observed after the injection of large doses of pitressin. This confirms the observation of Dodds and his associates.

REFERENCES

1. Oliver, G., and Schäfer, E. A.: On the Physiological Action of Extracts of Pituitary Body and Certain Other Glandular Organs, J. Physiol. **18**: 277, 1895.
2. Howell, W. H.: The Physiological Effects of Extracts of the Hypophysis Cerebri and Infundibular Body, J. Exper. Med. **3**: 245, 1898.
3. von Cyon, E.: Die physiologischen Herzgifte, Pflüger's Arch. f. d. ges. Physiol. **73**: 339, 1898.
4. Szymonowicz, Ladislaus: Die Function der Nebenniere, Pflüger's Arch. f. d. ges. Physiol. **64**: 97, 1896.
5. Schäfer, E. A., and Vincent, Swale: The Physiological Effects of Extracts of the Pituitary Body, J. Physiol. **25**: 87, 1899.
6. Garnier, M., and Thaon, P.: De l'action de l'hypophyse. Sur la pression artérielle et le rhythme cardiaque, J. de physiol. et de path. gén. **8**: 252, 1906.
7. Paukow, Otto: Über Wirkungen des "Pituitrin" (Parke, Davis & Co.) auf Kreislauf und Atmung, Pflüger's Arch. f. d. ges. Physiol. **147**: 89, 1912.
8. Führer, Hermann: Pharmakologische Untersuchungen über die wirksamen Bestandteile der Hypophyse, Ztschr. f. d. ges. exper. Med. **1**: 397, 1913.
9. Gruber, C. M.: The Blood Pressure in Unanesthetized Animals as Affected by "Vasopressin," "Oxytocin," Pituitary Extract and Other Drugs, J. Pharmacol. & Exper. Therap. **36**: 155, 1929.
10. Gruber, C. M., and Kountz, W. B.: II. Observations on the Effect of Pitressin on Blood Pressure, Pulse Rate and Respiration in Dogs, J. Pharmacol. & Exper. Therap. **39**: 275, 1930.
11. Goldenberg, M., and Rothberger, C. J.: Experimentelle Beiträge zur Theorie der Angina pectoris. I. Pitressinversuche. Ztschr. f. d. ges. exp. Med. **76**: 1, 1931.
12. de Bonis, Vittorio, and Susanna, Vittorio: Über die Wirkung des Hypophysenextraktes auf isolierte Blutgefässe, Zentralbl. f. Physiol. **23**: 169, 1909.
13. Pal: Quoted from Dale.

14. Cow, Douglas: Some Reactions of Surviving Arteries, J. Physiol. **42**: 125, 1911.
15. Rischbieter, Wilhelm: Das isolierte Kaninchenohr als überlebendes Gefässpräparat (nach Krawkow-Bissemski), zur Prüfung von Gefässmitteln, speziell Adrenalin und Hypophysin, Ztschr. f. d. ges. exper. Med. **1**: 355, 1913.
16. Geiling, E. M. K., Herrick, J. F., and Essex, H. E.: The Effect of Posterior Pituitary Preparations on the Blood Flow of the Normal Intact Dog, J. Pharmacol. & Exper. Therap. **51**: 18, 1934.
17. Dale, H. H.: The Action of Extracts of the Pituitary Body, Biochem. J. **4**: 427, 1909.
18. Meyer, Felix: Über die Wirkung verschiedener Arzneimittel auf die Coronargefässe des lebenden Tieres, Arch. f. Anat. u. Physiol. **223**: 258, 1912.
19. Rabe, F.: Die Reaction der Kranzgefässe auf Arzneimittel, Ztschr. f. exper. Path. u. Therap. **11**: 175, 1912.
20. Gunn, J. A.: The Action of Histamine on the Heart and Coronary Vessels, J. Pharmacol. & Exper. Therap. **29**: 325, 1926.
21. Gruber, C. M.: Some Observations on the Effect of Pituitary Extracts Upon Mammalian Coronary Vessels and Cardiac Muscle, AM. HEART J. **2**: 38, 1926.
22. Gruber, C. M., and Kountz, W. B.: Some Observations on the Effect of Pitressin Upon the Cardiovascular System, J. Pharmacol. & Exper. Therap. **39**: 435, 1930.
23. Morawitz, P., and Zahn, A.: Untersuchungen über den Coronarkreislauf, Deutsch. Arch. f. klin. Med. **116**: 364, 1914.
24. Bodo, Richard: The Effects of the "Heart-Tonics" and Other Drugs Upon the Heart-Tone and Coronary Circulation, J. Physiol. **64**: 365, 1928.
25. Rössler, Richard: Über experimentelle Herzchädigung durch Koronargefässverengerung und ihre Beeinflussung durch Pharmaka, Arch. f. exper. Path. u. Pharmakol. **153**: 1, 1930.
26. Ross, J. B., Dreyer, N. B., and Stehle, R. L.: The Cardiac Action of Pituitary Extract (Posterior Lobe), J. Pharmacol. & Exper. Therap. **38**: 461, 1930.
27. Anrep, G. V., and Stacey, R. S.: Comparative Effect of Various Drugs Upon the Coronary Circulation, J. Physiol. **64**: 187, 1927.
28. Häusler, H.: The Coronary Circulation. III. The Dependence of Changes in the Coronary Blood Flow on Cardiac and Local Vascular Factors, J. Physiol. **68**: 324, 1929.
29. Hochrein, Max: Der Coronarkreislauf, Berlin, 1932, Julius Springer.
30. Dietrich, Siegfried: Blutversorgung und Aktionsstrom des Herzens, Ztschr. f. d. ges. exper. Med. **90**: 689, 1933.
31. Essex, H. E., Wegria, R. G. E., Herrick, J. F., and Mann, F. C.: The Effect of Certain Drugs on the Coronary Blood Flow of the Trained Dog, AM. HEART J. **19**: 554, 1940.
32. Claude, H., Porak, R., and Routier, D.: Action cardiovasculaire de certains extraits hypophysaires. (Deuxième note), Compt. rend. Soc. de biol. **74**: 360, 1913.
33. Claude, H., Porak, R., and Routier, D.: L'action de l'extrait de lobe postérieur d'hypophyse sur la conductibilité auriculo-ventriculaire, Compt. rend. Soc. de biol. **74**: 996, 1913.
34. Hecht, A. F., and Nadel, Valerie: Experimentelle Untersuchungen über die Wirkung von Hypophysenextrakten mit Hilfe der Elektrokardiographie, Wien. klin. Wchnschr. **26**: 1927, 1913.
35. Resnik, W. H., and Geiling, E. M. K.: The Action of Pituitary Extract on the Heart of the Unanesthetized Dog, J. Clin. Investigation **1**: 217, 1925.
36. Gruber, C. M., and Kountz, W. B.: The Effect of Pitressin (Vaso-Pressin) Upon the Heart, Proc. Soc. Exper. Biol. & Med. **27**: 161, 1929.
37. Dearing, W. H., Barnes, A. R., and Essex, H. E.: Experiments With Calculated Therapeutic and Toxic Doses of Digitalis. II. Effects on the Electrocardiogram, AM. HEART J. **25**: 665, 1943.
38. Dearing, W. H., Barnes, A. R., and Essex, H. E.: Experiments With Calculated Therapeutic and Toxic Doses of Digitalis. I. Effects on the Myocardial Cellular Structure, AM. HEART J. **25**: 648, 1943.
39. Dodds, E. C., Noble, R. L., and Smith, E. R.: A Gastric Lesion Produced by an Extract of the Pituitary Gland, Lancet **2**: 918, 1934.
40. Dodds, E. C., Noble, R. L., Scarff, R. W., and Williams, P. C.: Pituitary Control of Alimentary Blood Flow and Secretion; Changes in the Stomach Produced by the Administration of Posterior Pituitary Extract, Proc. Roy. Soc., London **123**: 22, 1937.

EXPERIMENTS WITH CALCULATED THERAPEUTIC AND TOXIC DOSES OF DIGITALIS

VI. Comparative Effects of Toxic Doses of Digitalis and of Prolonged Deprivation of Oxygen on the Electrocardiogram, Heart, and Brain*

William H. Dearing, M.D.,† Arlie R. Barnes, M.D.,† and Hiram E. Essex, Ph.D.‡
Rochester, Minn.

THE purpose of this investigation was threefold: (1) to ascertain whether prolonged deprivation of oxygen would produce electrocardiographic changes which resembled those induced by toxic doses of digitalis; (2) to ascertain whether prolonged deprivation of oxygen was capable of producing histologic changes in the myocardium similar to those observed after the administration of toxic doses of digitalis; (3) to find out whether prolonged deprivation of oxygen and toxic doses of digitalis produced similar cellular alterations in the central nervous system.§

LITERATURE

The literature on deprivation of oxygen is immense. Much of it, although extremely interesting, is not strictly relevant to our problem. The basic contributions dealing with the effects of deprivation of oxygen on the electrocardiogram, the cellular structure of the myocardium, and the central nervous system will be mentioned.

Let us consider first the pertinent publications which describe changes in the RS-T segment and the T wave in the electrocardiogram after systemic deprivation of oxygen. Greene and Gilbert[1] reported a decrease of the amplitude of the T wave in the early stages (precrises) of deprivation of oxygen produced in young men during rebreathing experiments; sometimes the T wave was diphasic or negative near the stage of circulatory crisis. Greene and Gilbert[2] made similar observations on dogs. Miki[3] described the "church-spire" T wave of abnormal height in asphyxia. Kountz and Gruber[4] reported that a "high branching T wave" occurred in dogs which were connected with a rebreathing apparatus. This change in the T wave was observed when the oxygen saturation of the blood fell to less than 50 per cent of normal. These authors concluded that the high, branching T wave of coronary occlusion was due to anoxemia. Kountz and Hammouda[5] described

Received for publication Feb. 28, 1943.

*Abridgment of portion of thesis submitted by Dr. Dearing to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Ph.D. in Medicine.

†Division of Medicine, Mayo Clinic.
‡Division of Experimental Medicine, Mayo Foundation.

§The authors wish to express their appreciation to Dr. Walter M. Boothby for his aid in working out the technique.

changes in the RS-T segment and T wave when the right or left coronary artery in the canine heart-lung preparation was perfused with asphyxial blood. These authors concluded that the changes in the R-T segment after coronary occlusion were due to a high concentration of locally produced metabolites. Rothschild and Kissin[6] induced anoxemia in thirty-eight persons with a rebreathing apparatus. The electrocardiograms of ten of these showed a downward deviation of the S-T segment; one person had an upward deviation of the segment. An average of 7.9 per cent oxygen in the inspired air caused S-T changes in the controls, whereas an average of 8.4 per cent produced S-T deviations in the patients with angina pectoris.

Katz and Hamburger[7] reported a decrease in the height of the T wave and a depression of the S-T segment in studies on twenty normal persons who breathed air in which the oxygen was diminished gradually to 7 volumes per cent. Dietrich and Schwiegk[8] described in man, during deprivation of oxygen (8 per cent in inhaled air) a depression of RS-T_1 and RS-T_2, a negative T_2 and T_3, and an elevation of RS-T_2 and RS-T_3, associated with a depression of RS-T_1. Dietrich[9] observed, in dogs, flattening of the T wave, inversion of the T wave, or depression of the S-T segment. He showed that these electrocardiographic changes occurred when the oxygen in the inspired air ranged from 6 to 9 per cent and when the coronary blood flow, as measured by the Rein thermostromuhr, was increased considerably. Cluzet, Piéry, Ponthus, and Milhaud[10] described an elevation of the T wave in dogs in a low pressure chamber. Tigges[11] observed a flattening of the T wave in normal persons who were subjected to hypoxemia. Larsen[12] administered 9 per cent oxygen to ninety persons, in some of whom he found a depression of the S-T segment, flattening of the T wave, and inversion of the T waves. Borgard[13] reported flattening of the T waves, with a transition to negative T waves; finally, the T wave became high and spiked. These studies were done on animals at low atmospheric pressures. Levy, Baraeh, and Bruenn[14] and Levy, Bruenn, and Russell[15] described a flattening of the T wave and occasional depression of the RS-T segment in persons who inhaled 10 per cent oxygen and 90 per cent nitrogen. May[16] made similar observations on normal persons.

Binet, Strumza, and Ordóñez[17] observed in dogs that a negative T_2 occurred when 7.36 per cent oxygen was inhaled, and an elevation of the R-T segment, along with a tall T wave, appeared when 2.41 or 2.89 per cent oxygen was administered. Scott, Leslie, and Mulinos[18, 19] subjected cats to atmospheres containing 10 per cent oxygen both before and after ligation of the left branch of the anterior descending coronary artery. The RS-T segment did not deviate from its isoelectric position with anoxemia preoperatively. After the coronary artery had been ligated, the RS-T segment was deviated upward; in time, the RS-T segment returned to the isoelectric position, even though the infarct persisted.

When the animals then were subjected to anoxemia, the RS-T segment assumed the deviation pattern which occurred just after the coronary artery had been ligated. Levy, Bruenn, and Williams[20] stated that, among patients suffering from angina pectoris and coronary sclerosis, changes in the RS-T segment and the T wave developed after the administration of digitalis (1.5 Gm. in four days). These changes resembled those caused by anoxemia.[14, 15] On the fifth day, anoxemia was produced in these digitalized patients; it was found that the deviation of the RS-T segment diminished by 40 per cent, and the interval between the production of anoxemia and the time of appearance of the pain was shortened 9 per cent. The latter observation agrees with the contention of Gilbert and Fenn[21] that digitalis increases the susceptibility to pain of patients suffering from angina pectoris. Gold, Otto, Kwit, and Satchwell,[22] on the contrary, stated that the likelihood that digitalis will produce angina is negligible.

Concerning the effects of systemic anoxia on the anatomic structure of the heart, several references were found in the literature. Schrötter[23] observed fatty degeneration in the myocardiums of guinea pigs which were subjected to low atmospheric pressures (230 mm. Hg) for forty hours. Campbell[24] also noted fatty changes in the myocardiums of cats, rabbits, calves, and mice after they had been exposed for a long time to low oxygen pressures. Luft[25] observed necrosis in the papillary muscle and in the left ventricular wall of the hearts of guinea pigs which had been subjected to low pressures (230 to 300 mm. Hg for 120 to 180 hours). For the sake of completeness, it may be worth while to mention that Büchner[26] produced necrosis of the myocardium in anemic, exercised rabbits, and that Liebmann,[27] Herzog,[28] Gey,[29] Gürich,[30] Tesseraux,[31] Kroetz,[32] Nagel,[33] and many others have described myocardial degeneration in man after poisoning by illuminating gas. Although the myocardial lesions produced by either coronary occlusion in man or coronary ligation in animals are too familiar to warrant comment, it might be of interest to point out that Tennant, Grayzel, Sutherland, and Stringer[34] did not observe anatomic changes in the myocardium until eight hours or more after coronary ligation. Karsner and Dwyer[35] described histologic changes twelve hours after permanent ligation of the coronary artery.

Some of the major contributions on the effects of deprivation of oxygen on the central nervous system will now be reviewed. Deprivation of oxygen has been produced in the central nervous system by temporary ligation of blood vessels, by the use of low pressure chambers, and by the inhalation of air of low oxygen content. de Buck and de Moor,[36] Mott,[37, 38] Hill and Mott,[39] Gomez and Pike,[40] and Gildea and Cobb[41] described cellular changes of the central nervous system after ligation of blood vessels. The changes in the nerve cells consisted of chromatol-

ysis, swelling of the cells, shrinkage of the cells, vacuolization of the cytoplasm, neuronophagia, and complete disintegration of the cells. Gildea and Cobb described foci of necrosis in the brains of their cats after temporary ligation of the cerebral vessels; they found that ten minutes of cerebral ischemia was sufficient to damage cortical cells permanently. Martin, Loevenhart, and Bunting[42] exposed rabbits to low oxygen tension (average oxygen percentage = 7.21 to 7.98) for twelve to 231 hours. They did not find any anatomic changes in the brain or spinal cord. Ford[43] asphyxiated cats and kittens by washing the air from a bell jar with nitrogen; then the animals were resuscitated and finally killed. No lesions were found in the brain. Büchner and Luft[44] described degenerative changes in the brains of guinea pigs which were subjected to low atmospheric pressures (250 to 300 mm. Hg) from 103 to 133½ hours.

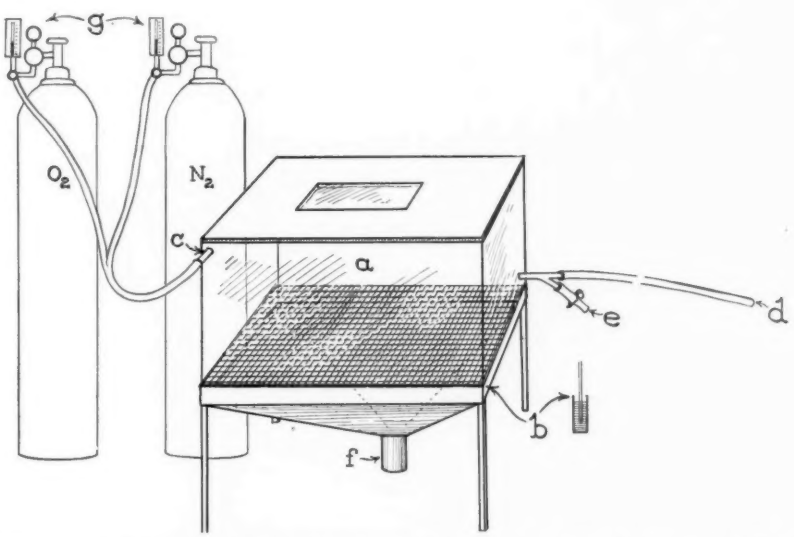

Fig. 1.—Diagram illustrating the apparatus used to attain low percentages of oxygen over long periods (days). *a*, Water-sealed chamber with wire cage floor; *b*, cross section showing the structure of the water-sealed border of the chamber; *c*, tube through which the gas mixture flowed into the chamber; *d*, tube, 6 feet (183 cm.) long, through which the gas mixture flowed from the chamber; *e*, side tube through which samples of gas were collected; *f*, sealed glass jar in which urine was collected; *g*, Heidbrink flowmeters connected to the oxygen and nitrogen tanks.

METHODS

Six cats were used in these studies on deprivation of oxygen. The animals were placed in a large, water-sealed chamber (Fig. 1), and breathed oxygen at low concentrations for several days. The desired concentration of oxygen was attained and maintained by allowing mixtures of oxygen and nitrogen to flow continuously into the upper portion of one end of the chamber and to flow out through the lower portion of the opposite end of the chamber. Influx of atmospheric air into the chamber was prevented by attaching a rubber tube, 6 feet (183 cm.) long and of small caliber, to the outflow opening.

The percentage of oxygen in the chamber was adjusted by controlling the rate of inflow of the nitrogen and oxygen through calibrated flowmeters attached to each gas tank. For example, if the nitrogen flowed at the rate of 9.5 liters per minute and the oxygen at 0.5 liters per minute, then the proportion of oxygen entering the chamber would be approximately 5 per cent ($\frac{0.5}{9.5 + 0.5} = 0.05$ or 5 per cent). These calculations permitted one to estimate quickly the percentage of oxygen at any moment during the experiment.

Samples of gas were collected at various intervals through a side tube placed near the outflow opening of the chamber. The percentages of oxygen and carbon dioxide were ascertained in these samples with the Haldane gas analyzer. The percentages of oxygen as calculated from the rates of flow of nitrogen and oxygen through the flowmeters agreed fairly well with those ascertained by actual analysis. The carbon dioxide was prevented from accumulating by maintaining a fairly rapid flow of nitrogen and oxygen through the chamber; therefore, absorption of the carbon dioxide with soda lime was not necessary. The content of carbon dioxide in the chamber varied from 0.2 to 0.6 per cent.

The cats lay on the right side while electrocardiograms were made at various intervals throughout the course of the experiment. The electrocardiographic lead wires traversed the outflow tube described previously.

The cats were removed from the chamber for a short time each morning to permit cleaning of the chamber, feeding of the animals, and readjustment of the electrocardiographic electrodes on their extremities. The electrocardiograms were taken as described elsewhere.[45]

Notes were made on the appearance and behavior of the animals while they inhaled the low-oxygen gas mixture.

The animals which did not die spontaneously were killed in an ether or chloroform chamber after they had inhaled the low-oxygen mixtures for three to eight days. The heart, brain, spinal cord, stomach, duodenum, ileum, uterus, biceps, diaphragm, and abdominal musculature were prepared for microscopic study in accordance with the procedure described in a previous paper.[46]

The control animals for the microscopic studies were the same as those described elsewhere.[46]

TABLE I

CORRELATION OF DURATION OF SYSTEMIC DEPRIVATION OF OXYGEN AND HISTOLOGIC STUDIES OF THE MYOCARDIUM

AVERAGE OXYGEN, PER CENT	MINIMAL OXYGEN, PER CENT	DURATION OF EXPERIMENT	HISTOLOGIC CHANGES					REMARKS
			PAPILLARY MUSCLE AND LEFT VENTRICLE	INTERVENTRICULAR SEPTUM	RIGHT VENTRICLE	LEFT ATRIUM	RIGHT ATRIUM	
4.43	4.43	1½ hours	No	No	No	No	No	Died
4.54	4.36	3 days	Yes +++	Yes +++	Yes ++	Yes +	Yes +	Extensive lesions
4.82	3.54	4 days	Yes ++	Yes ++	Yes +	?	?	Extensive lesions
5.29	4.36	4 days	Yes +	Yes +	Yes +	?	±	Extensive lesions
4.86	4.58	5 days	Yes +++	Yes ++	Yes +	Yes +	Yes +	Moderately extensive lesion
4.71	4.36	8 days	Yes +	Yes +	Yes ±	No	No	Few lesions

RESULTS

A. Anatomic Studies of the Myocardium After Prolonged Systemic Deprivation of Oxygen.—It will be recalled that the myocardiums of the control animals did not reveal any evidence of degenerative changes.

Table I indicates the effects of prolonged systemic deprivation of oxygen on the myocardium in our experimental animals. There were no changes in the myocardium of the animal which died one and a half hours after the inhalation of low concentrations of oxygen, whereas the five animals which survived three or more days in the low-oxygen gas mixture exhibited varying degrees of histologic change in the myocardium.

Fig. 2.—Degenerative changes in the myocardium after prolonged systemic deprivation of oxygen (×450).

The anatomic lesions produced in the myocardium after prolonged exposure to low-oxygen tensions differed very little from those which were seen after the injection of toxic doses of digitalis (compare Fig. 2 with Fig. 1 of the first paper of this series).[46] The lesions produced by digitalis were, as a rule, more extensive than those that occurred after deprivation of oxygen. The earliest definite and obvious change in the myocardium after prolonged anoxia was degeneration of the muscle fibers in localized zones (Fig. 2). In time, cellular degeneration, plus exudative cells, was present in the myocardium. These histologic changes

were apparently not different from those produced by the administration of digitalis or pitressin, coronary ligation, and so forth.

The cellular changes were most prominent and extensive in the papillary muscle, the left ventricular wall, and the interventricular septal wall. Except in two animals, the atrial and auricular anatomic changes were either absent or difficult to recognize.

The old animals died sooner and showed more extensive myocardial lesions than the young ones. For example, an old cat died spontaneously after three days of deprivation of oxygen, and its heart contained extensive degenerative changes, while a young adult cat lived for eight days at low oxygen tensions; it was killed on the eighth day, and its heart showed only a few degenerative lesions. This difference of sensitivity to deprivation of oxygen was not because of arteriosclerosis in the older animal, for no evidence of this disease was observed in the coronary arteries or arterioles of any of our experimental animals.

TABLE II

CORRELATION OF DURATION OF SYSTEMIC DEPRIVATION OF OXYGEN, HISTOLOGIC STUDIES OF THE MYOCARDIUM, AND THE MOST PROMINENT CHANGE IN RS-T SEGMENT AND T WAVE OBSERVED DURING THE EXPERIMENT

AVERAGE OXYGEN, PER CENT	MINIMAL OXYGEN, PER CENT	DURATION OF EXPERIMENT	HISTOLOGIC CHANGE IN MYOCARDIUM	MOST PROMINENT CHANGE OF RS-T SEGMENT AND T WAVE OBSERVED
4.43	4.43	1½ hours	No	Negative T_1
4.54	4.36	3 days	Yes	Cove-plane, negative T_2 and T_3; T_1 flattened but positive
4.82	3.54	4 days	Yes	Depression RS-T_1, RS-T_2 and RS-T_3; finally cove-plane negative T_2 and T_3
4.86	4.58	5 days	Yes	Depression RS-T_1, RS-T_2 and RS-T_3; finally cove-plane negative T_2 and T_3
4.71	4.36	8 days	Yes	Depression RS-T_1, RS-T_2 and RS-T_3

B. Electrocardiographic Studies During Prolonged Systemic Deprivation of Oxygen.—The changes in the RS-T segment and T wave observed after deprivation of oxygen (Table II) were as follows: (1) decrease in the height of the T wave in one or more leads, usually in all three leads; (2) increase in the height of the T wave in one or more leads; (3) inversion of the T wave in one, two, or three leads; (4) depression of the RS-T segment in one or more leads; (5) cove-plane, negative T_2 and T_3; (6) negative T_1 and positive T_3.

The RS-T segment was not elevated significantly (plateau type) in any of the electrocardiograms which were made while the animals were inhaling low-oxygen gas mixtures. It is not known whether the segments would have become elevated if the animals had been permitted to remain out of the low-oxygen chamber for a day or so after myocardial lesions had developed.

The succession of electrocardiographic changes was usually initiated by decreases in the height of the T waves, and sometimes by a negative

T_3; then either tall T waves or simply inverted T waves in one or more leads were observed; depression of the RS-T segments, with diphasic T waves in one or more leads (Fig. 3), was noted to precede or follow the tall T waves or the simply inverted T waves; finally, cove-plane,

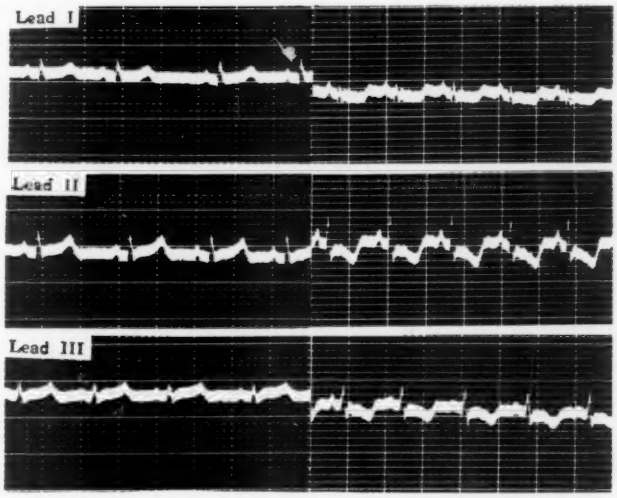

Fig. 3.—On the left, control electrocardiogram; on the right, depression of the RS-T segment after systemic deprivation of oxygen.

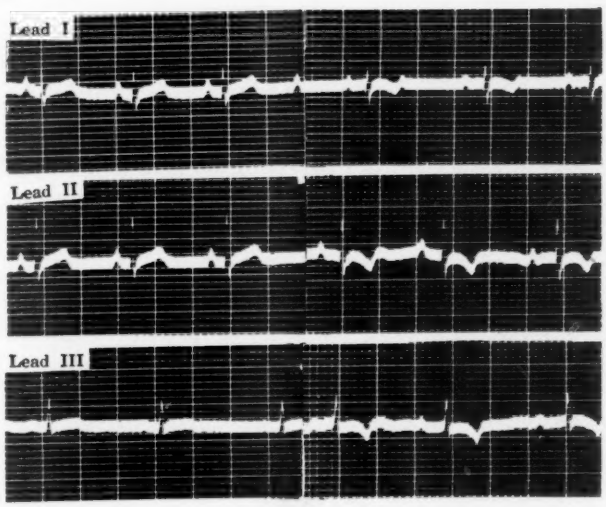

Fig. 4.—On the left, control electrocardiogram; on the right, cove-plane, negative T_2 and T_3 after prolonged deprivation of oxygen. Myocardial lesions were associated with this pattern.

negative T_2 and T_3, with flattened T_1 and diphasic T_1, preceded by a depressed RS-T_1 segment, were observed (Fig. 4). When the animals were permitted to breathe atmospheric air, the foregoing electrocardiographic changes were altered promptly or reverted to the normal pattern.

Many other electrocardiographic changes were observed during the various grades of anoxia: sinus tachycardia, sinus bradycardia, prolongation of the Q-T interval, heart block, decreased height of the QRS complex, flattening of the P wave, and so forth.

C. Anatomic Studies of the Brain and Spinal Cord After Prolonged Systemic Deprivation of Oxygen.—The central nervous systems of only three of our six experimental animals were examined microscopically (Table III). The cerebral cortex (frontal, motor, and visual), the cerebellum, the pons, and the spinal cord (cervical, thoracic, and lumbar) were the portions of the nervous system studied. The cerebral cortex was the most vulnerable to deprivation of oxygen. Degenerative lesions were observed in the cortices of all three animals. The cerebellum of one animal showed a few pyknotic and vacuolated cells. The pons in two animals contained scattered pyknotic and vacuolated cells. No evidence of degeneration was seen in any of the cells in the spinal cord.

TABLE III

CORRELATION OF DURATION OF SYSTEMIC DEPRIVATION OF OXYGEN AND STUDIES ON THE CELLULAR STRUCTURE OF THE CENTRAL NERVOUS SYSTEM

AVERAGE OXYGEN, PER CENT	MINIMAL OXYGEN, PER CENT	DURATION OF EXPERIMENT	HISTOLOGIC CHANGES				REMARKS
			CEREBRUM	CEREBELLUM	PONS	SPINAL CORD	
4.43	4.43	1½ hours	No	No	No	No	Died
4.54	4.36	3 days	–	–	–	–	Died
4.82	3.54	4 days	Yes +++	±	±	No	Extensive lesions
5.29	4.36	4 days	–	–	–	–	Died
4.86	4.58	5 days	Yes +++	No	±	No	Moderately extensive lesions
4.71	4.36	8 days	Yes +±	No	No	No	Few lesions

The type of changes observed in the large and small pyramidal cells of the cerebral cortex may be summarized as follows: (1) swelling; (2) pyknosis; (3) vacuolization; (4) degeneration (necrosis); and (5) satellitosis.

The cellular changes were essentially the same as those described after digitalis had been administered in toxic amounts. The lesions produced by digitalis were far more extensive and intensive than those produced by deprivation of oxygen. Fig. 5 illustrates the degenerative changes in the pyramidal cells after prolonged deprivation of oxygen.

D. Signs Observed in Animals While They Were Subjected to Systemic Deprivation of Oxygen.—An endeavor was made to keep the percentage of oxygen in the chamber at a level which produced only slight drowsiness in the animals. The cats seemed to breathe 4 to 5 per cent oxygen without much evidence of distress. When the percentage of oxygen fell too rapidly or was held at too low a level, the animals became restless and exhibited a panting type of respiration.

Sometimes cyanosis of the tip of the nose and tongue was observed. Vomiting occurred on two occasions. Ataxia was noted in several of

the animals when they were removed from the chamber for the daily feeding. This ataxia did not persist very long. Death occurred as the result of respiratory failure in three cats; electrocardiograms were taken on these three animals when death occurred—the respirations ceased before the heart stopped beating.

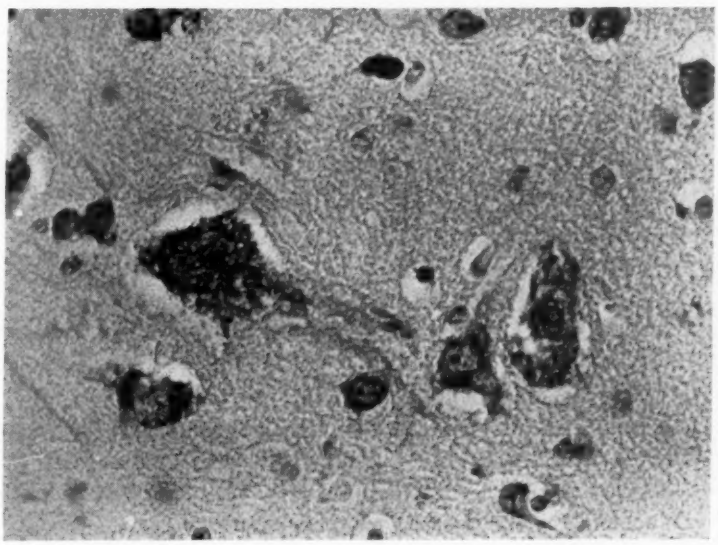

Fig. 5.—Degeneration of the pyramidal cells of the cerebral cortex after prolonged deprivation of oxygen (×450).

At any given low percentage of oxygen, the old animals showed more tendency to cyanosis and panting respiration than did the young animals. The old cats died sooner than the young ones while breating the same percentage of oxygen.

COMMENT

The experimental methods used in these studies were simple and readily controlled. The percentage of oxygen was checked by two independent methods. The necropsies were done immediately after the animals died or were killed. The myocardial and cerebral degenerative changes had to be definite before we counted them as myocardial or cerebral lesions. This avoided quibbling about borderline intracellular morphologic changes.

In order to avoid errors in the interpretation of these experimental results, it should be pointed out that these animals were subjected to rather severe grades of anoxia over long periods. We do not know how the cat and man compare in their relative sensitization to deprivation of oxygen. We wish to avoid giving the impression that, just because the electrocardiographic, myocardial, and cerebral changes after prolonged deprivation of oxygen resembled those seen after the admin-

istration of toxic doses of digitalis, the lesions produced by digitalis were the result of anoxia and nothing else. This conclusion is unwarranted. The fact that deprivation of oxygen may produce changes similar to those induced by toxic doses of digitalis may be interpreted as possible presumptive evidence, but certainly not as direct proof, that anoxemia may be one of the many factors involved in the production of myocardial and cerebral lesions by digitalis.

In order to avoid another error of interpretation, it may be worth while to emphasize that existing experiments of short duration (done by others) indicate that anoxia dilates the coronary arteries and increases the coronary blood flow.

SUMMARY

Histologic changes were observed in the myocardiums of animals which were subjected to prolonged systemic deprivation of oxygen over periods of three or more days. An endeavor was made to keep the concentration of oxygen near 4 to 5 per cent. One animal, which died one and a half hours after the inhalation of low percentages of oxygen, did not show any evidence of anatomic changes in the myocardium.

The myocardial lesions produced by deprivation of oxygen resembled those found in the heart after the administration of toxic doses of digitalis. They were focal in distribution and were most prominent in the papillary muscle and in the left ventricular wall.

The following is a summary of the prominent changes in the RS-T segment and the T wave after prolonged systemic deprivation of oxygen: (1) decrease or increase in the height of the T waves in one or more leads, (2) simple inversion of the T waves in one or more leads, (3) depression of the RS-T segment in one or more leads, (4) cove-plane, negative T_2 and T_3, and (5) negative T_1 and positive T_3.

The electrocardiographic changes, as a rule, disappeared when atmospheric air was introduced into the chamber.

Cellular changes were observed in the central nervous system after prolonged deprivation of oxygen. The changes were similar to those described by others after anoxia and to those observed after the administration of toxic doses of digitalis.

Old animals were more sensitive to deprivation of oxygen than young ones.

REFERENCES

1. Greene, C. W., and Gilbert, N. C.: Studies on the Responses of Circulation to Low Oxygen Tension. III. Changes in the Pacemaker and in Conduction During Extreme Oxygen Want as Shown in the Human Electrocardiogram, Arch. Int. Med. **27**: 517, 1921.
2. Greene, C. W., and Gilbert, N. C.: Blood Pressure and Electrocardiographic Changes in the Dog During Extreme Oxygen Want, Am. J. Physiol. **55**: 307, 1921.
3. Miki, Y.: Experimentelle und klinische Untersuchungen über die Dauer des K-Ekg. (Kammer-Elektrokardiogramms), Ztschr. f. d. ges. exper. Med. **27**: 323, 1922.

4. Kountz, W. B., and Gruber, C. M.: The Electrocardiographic Changes in Anoxemia, Proc. Soc. Exper. Biol. & Med. **27**: 170, 1929.
5. Kountz, W. B., and Hammouda, M.: Effect of Asphyxia and Anoxemia on the Electrocardiogram, AM. HEART J. **8**: 259, 1932.
6. Rothschild, M. A., and Kissin, Milton: Induced General Anoxemia Causing S-T Deviation in the Electrocardiogram, AM. HEART J. **8**: 745, 1933.
7. Katz, L. N., and Hamburger, W. W.: Effect of Anoxemia on the Electrocardiogram of Normal Persons, J. A. M. A. **100**: 141, 1933.
8. Dietrich, S., and Schwiegk, H.: Das Schmerzproblem der Angina Pectoris, Klin. Wchnschr. **12**: 135, 1933.
9. Dietrich, Siegfried: Blutversorgung und Aktionsstrom des Herzens, Ztschr. f. d. ges. exper. Med. **90**: 689, 1933.
10. Cluzet, Piéry, Ponthus, P., and Milhaud: Sur les modifications de l'électrocardiogramme chez l'animal soumis aux fortes dépressions barométriques, en chambre pneumatique, Lyon méd. **156**: 182, 1935.
11. Tigges, Franz: Das Elektrokardiogramm bei Hypoxämie, Ztschr. f. Kreislaufforsch. **28**: 225, 1936.
12. Larsen, Kaj: Effect of Anoxemia on the Human Electrocardiogram, Acta med. Scandinav. Suppl. **78**: 141, 1936.
13. Borgard, Werner: Ergebnisse elektrokardiographischer Untersuchungen bei Erniedrigung des atmosphärischen Druckes, Arbeitsphysiol. **9**: 308, 1936.
14. Levy, R. L., Barach, A. L., and Bruenn, H. G.: Effects of Induced Oxygen Want in Patients With Cardiac Pain, AM. HEART J. **15**: 187, 1938.
15. Levy, R. L., Bruenn, H. G., and Russell, N. G.: The Use of Electrocardiographic Changes Caused by Induced Anoxemia as a Test for Coronary Insufficiency, Am. J. M. Sc. **197**: 241, 1939.
16. May, S. H.: Electrocardiographic Response to Gradually Induced Oxygen Deficiency; Response of Normal Hearts in Various Age Groups, AM. HEART J. **17**: 655, 1939.
17. Binet, Léon, Strumza, M. V., and Ordóñez, J. H.: Coeur et anoxie, Arch. d. mal. du coeur **31**: 11, 1938.
18. Leslie, Alan, Scott, W. S., Jr., and Mulinos, M. G.: Effect of Anoxemia Upon Electrocardiogram of Cats After Coronary Ligation, Proc. Soc. Exper. Biol. & Med. **41**: 652, 1939.
19. Scott, W. S., Jr., Leslie, Alan, and Mulinos, M. G.: Studies on Coronary Occlusion. I. The Effects on the Electrocardiogram of the Cat of Producing Anoxemia After Coronary Artery Ligation, AM. HEART J. **19**: 719, 1940.
20. Levy, R. L., Bruenn, H. G., and Williams, N. E.: The Modifying Action of Certain Drugs (Aminophyllin, Nitrites, Digitalis) Upon the Effects of Induced Anoxemia in Patients With Coronary Insufficiency; With Remarks on Therapy, AM. HEART J. **19**: 639, 1940.
21. Gilbert, N. C., and Fenn, G. K.: Effect of Digitalis on the Coronary Flow, Arch. Int. Med. **50**: 668, 1932.
22. Gold, Harry, Otto, Harold, Kwit, N. T., and Satchwell, Harry: Does Digitalis Influence the Course of Cardiac Pain? A Study of 120 Selected Cases of Angina Pectoris, J. A. M. A. **110**: 859, 1938.
23. Schrötter, Hermann v.: Über Schädigungen des Organismus bei Verminderung des äusseren Luftdruckes, Verhandl. d. deutsch. path. Gesellsch. Fünfte Tagung, 1902.
24. Campbell, J. A.: Note on Some Pathological Changes in the Tissues During Attempted Acclimatization to Alterations of O_2-Pressure in the Air, Brit. J. Exper. Path. **8**: 347, 1927.
25. Luft, U. C.: Irreversible Organveränderungen durch Hypoxämie im Unterdruck, Beitr. z. path. Anat. u. z. allg. Path. **98**: 323, 1937.
26. Büchner, Franz: Das morphologische Substrat der Angina pectoris im Tierexperiment, Beitr. z. path. Anat. u. z. allg. Path. **92**: 311, 1933.
27. Liebmann, Ehrich: Ein Fall von Herzmuskelentzündung nach Leuchtgasvergiftung, Deutsche med. Wchnschr. **2**: 1192, 1919.
28. Herzog, G.: Zur Pathologie der Leuchtgasvergiftung mit makro- und mikroskopischen Demonstrationen, München. med. Wchnschr. pt. 1 **67**: 558, 1920.
29. Gey, Rudolf: Zur pathologischen Anatomie der Leuchtgasvergiftung, Virchows Arch. f. path. Anat. **251**: 95, 1924.
30. Gürich: Herzmuskelveränderungen bei Leuchtgasvergiftung, München. med. Wchnschr. pt. 2, **72**: 2194, 1925.
31. Tesseraux, Hans: Ueber ausgedehnte Myokardnekrosen bei einem Fall von Leuchtgasvergiftung, Centralbl. f. allg. Path. u. path. Anat. **42**: 344, 1928.

32. Kroetz, C.: Herzschädigungen nach Kohlenoxydvergiftungen, Deutsche med. Wchnschr. **2**: 1365, 1936.
33. Nagel, H. G.: Zur Frage der Koronarschädigungen nach Leuchtgasvergiftungen, Deutsche med. Wchnschr. **1**: 301, 1937.
34. Tennant, Robert, Grayzel, D. M., Sutherland, F. A., and Stringer, S. W.: Studies on Experimental Coronary Occlusion. Chemical and Anatomical Changes in the Myocardium After Coronary Ligation, AM. HEART J. **12**: 168, 1936.
35. Karsner, H. T., and Dwyer, J. E.: Studies in Infarction. IV. Experimental Bland Infarction of the Myocardium, Myocardial Regeneration and Cicatrization, J. M. Research **34**: 21, 1916.
36. de Buck and de Moor: Quoted by Gomez, Liborio, and Pike, F. H.
37. Mott, F. W.: The Degeneration of the Neurone, Lancet **1**: 1779, 1900.
38. Mott, F. W.: The Degeneration of the Neurone, Lancet **1**: 1849, 1930.
39. Hill, Leonard, and Mott, F. W.: The Neuro-Fibrils of the Large Ganglion Cells of the Motor Cortex of Animals in Which the Four Arteries Had Been Ligatured to Produce Cerebral Anaemia, J. Physiol. **34**: IV, 1906.
40. Gomez, Liborio, and Pike, F. H.: The Histological Changes in Nerve Cells Due to Total Temporary Anaemia of the Central Nervous System, J. Exper. Med. **11**: 257, 1909.
41. Gildea, E. F., and Cobb, Stanley: The Effects of Anaemia on the Cerebral Cortex of the Cat, Arch. Neurol. & Psychiat. **23**: 876, 1930.
42. Martin, H. G., Loevenhart, A. S., and Bunting, C. H.: The Morphological Changes in the Tissues of the Rabbit as a Result of Reduced Oxidation, J. Exper. Med. **27**: 399, 1918.
43. Ford, F. R.: An Experimental Investigation Into the Effects of Asphyxia on the Brain, With Especial Reference to Asphyxia Neonatorum, Bull. Johns Hopkins Hosp. **42**: 70, 1928.
44. Büchner, Franz, and Luft, Ulrich: Hypoxämische Veränderungen des zentralnervensystems im Experiment, Beitr. z. path. Anat. u. z. allg. Path. **96**: 549, 1936.
45. Dearing, W. H., Barnes, A. R., and Essex, H. E.: Experiments With Calculated Therapeutic and Toxic Doses of Digitalis. II. Effects on the Electrocardiogram, AM. HEART J. **25**: 665, 1943.
46. Dearing, W. H., Barnes, A. R., and Essex, H. E.: Experiments With Calculated Therapeutic and Toxic Doses of Digitalis. I. Effects on the Myocardial Cellular Structure, AM. HEART J. **25**: 648, 1943.

Clinical Report

INTRAPERICARDIAL ANEURYSM CAUSED BY CONGENITAL SYPHILIS

C. Dominguez, R. F. Schärer, and E. R. Pietrafesa
Buenos Aires, Argentina

AS POINTED out by Moore,[1] "cardiovascular lesions happen so rarely in congenital lues that they can be discarded as practically non-existent." For this reason, we feel that it is worth while to present the clinical and post-mortem observations on an 18-year-old girl who showed clear-cut signs of aortic insufficiency of the Hodgson type and aneurysm of the ascending aorta caused by congenital syphilis.

CASE REPORT

History.—Both parents are alive. The mother has had repeatedly positive blood Wassermann and Kahn reactions, and has aortic insufficiency of the Hodgson type and marked dilatation of the ascending aorta. She has had ten pregnancies, of which the first four were successful, and the offspring are alive and healthy; the fifth was spontaneously interrupted by abortion after seven months; the sixth was successful, and this offspring is our patient; the seventh was interrupted by abortion after eight months; and from the other three pregnancies, which were successful, two children died in infancy and one is alive and in good health. We were not able to examine any other relative of our patient.

At the age of 3 years, our patient was ill with what was diagnosed as meningitis. However, from that time until the beginning of the illness described in this paper, she felt well. For two weeks before her admission to the hopital, she had nocturnal paroxysmal dyspnea on exertion, together with retrosternal pain and cough.

Physical examination.—Adenoidal facies and inadequate nutrition. Cardiovascular system: pulse regular, equal, and forcible. Blood pressure: 120/20. Forcible arterial pulsations in the neck. Apex beat in the sixth left intercostal space outside the mammillary line, with elevation of the thoracic wall. A marked thrill was felt in the second and third right intercostal spaces, where there was a double murmur (systolic and diastolic) which was transmitted to the rest of the precordial area; the systolic component was the more intense. The heart sounds were normal.

The rest of the physical examination was negative. The blood Wassermann and Kahn reactions were positive; the blood urea nitrogen and glucose were normal, as was the urine.

Roentgenologic examination showed a heart of mitral-aortic configuration, markedly enlarged (Fig. 1). The ascending aorta made a

Medical Clinic, Rivadavia Hospital.

bulge to the right, and the auriculovascular point was lowered. The superior vena cava was distended. The pulsations of the left ventricle were of the excited type, and those of the ascending aorta were expansile. In the left oblique posterior view the considerable enlargement of the ascending aorta, with its expansile pulsation, and the enlargement of the left ventricle were verified. The lateral view showed marked enlargement of the anteroposterior diameter of the heart and disappearance of the retrosternal clear space as a result of the aortic enlargement. By means of a radiopaque meal, it was found that the entire esophagus was deflected backwards. There was a marked pulmonary design, and the right hilum was covered by the shadow of the ascending aorta.

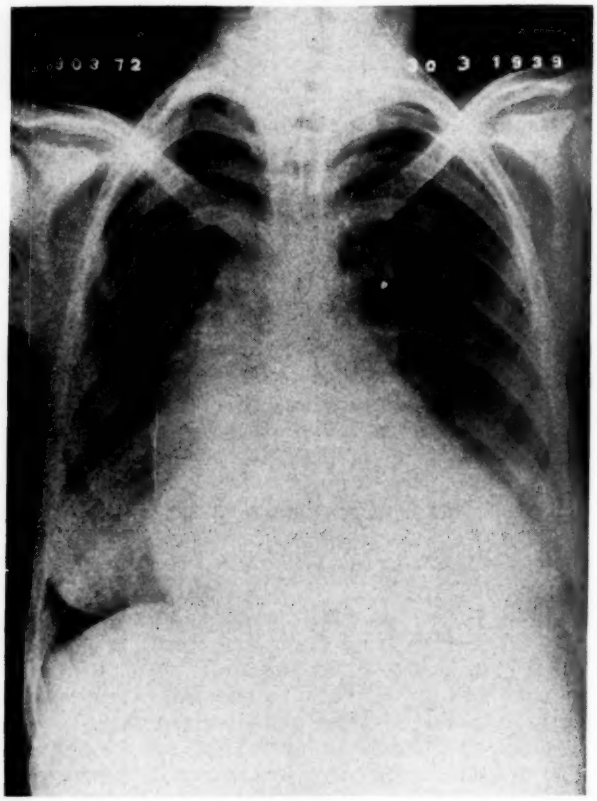

Fig. 1.

The electrocardiogram showed sinus tachycardia and bundle branch block of the common type.

Treatment, consisting of the administration of bismuth carbonate and cardiotonics, was begun. The patient improved only slightly, and, after two and one-half months, suffered again with nocturnal paroxysmal dyspnea and died during an attack of cardiac asthma.

Necropsy.—Macroscopically, it was found that the heart was enlarged, particularly the left ventricle, which showed evident hypertrophy and dilatation of both inflow and outflow paths (Fig. 2). There were marked retraction and hardening of the aortic sigmoid valves; and a fusiform

aneurysm of the whole ascending aorta, of a size somewhat greater than a hen's egg, was found (Fig. 2, *a*). The pericardium at that level was somewhat thickened.

Microscopic examination was performed by Dr. M. A. Etcheverry, who reported the following: The root of the aorta immediately above the region of the annulus (Fig. 3), and especially along the wall of the vessel upwards nearer the aneurysmal dilatation (Fig. 4), showed thinness and fibroid transformation of the intima, the limits of which with the media were not clear; the elastic tissue of the media was disorganized and dissociated by thin bundles of fibroid tissue in large zones; the adventitia was thickened and discretely sclerosed; its small blood vessels had a decreased diameter and thickened walls.

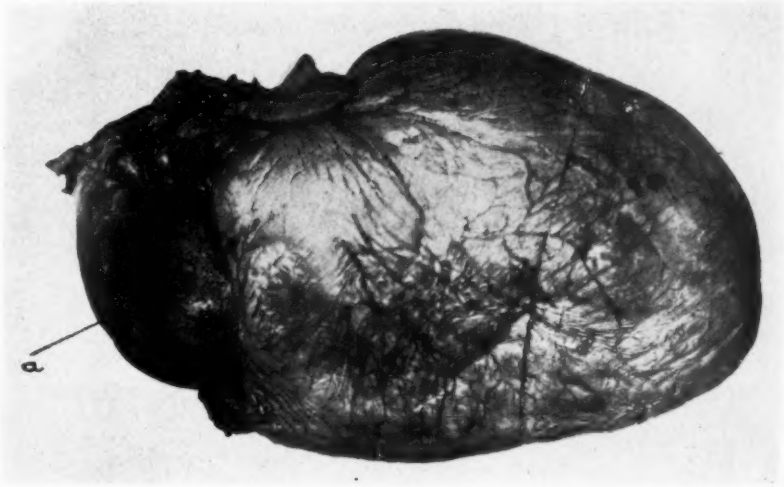

Fig. 2.

At the level of the aneurysmal dilatation (Fig. 5), the lesions were even more pronounced. The aortic wall was thinner, and all of its layers were affected. The intima was thinner, fibrous, and had deposits of hematic pigment. The limits with the media were confused. The latter was also thin, and its musculoelastic tissue was markedly dissociated and disorganized by thick bands of hyalinized fibrous tissue. This fibrous replacement was particularly marked in the external part of the media, where, sometimes, the border of the adventitia was barely indicated by a tenuous band of fibroelastic tissue; it was not of nodular character, but in the form of long longitudinal bands, more or less large in different places. The adventitia showed its greatest thickness in this area; in some parts it formed nearly half of the wall of the aorta. There was also sclerosis; large collagenous bundles, partially hyalinized, and arranged in an undulate form parallel to the axis of the vessel, were present, and a few fibrocyte nuclei were visible. No Aschoff's nodules were to be seen. The vessels of the adventitia were scarce; their walls were thick and fibrous, and their lumina were narrow or even obliterated. Around some of them a few leucocytes were seen, predominantly lymphocytes and plasmocytes. Nowhere did the sclerosis of the adventitia acquire a nodular aspect.

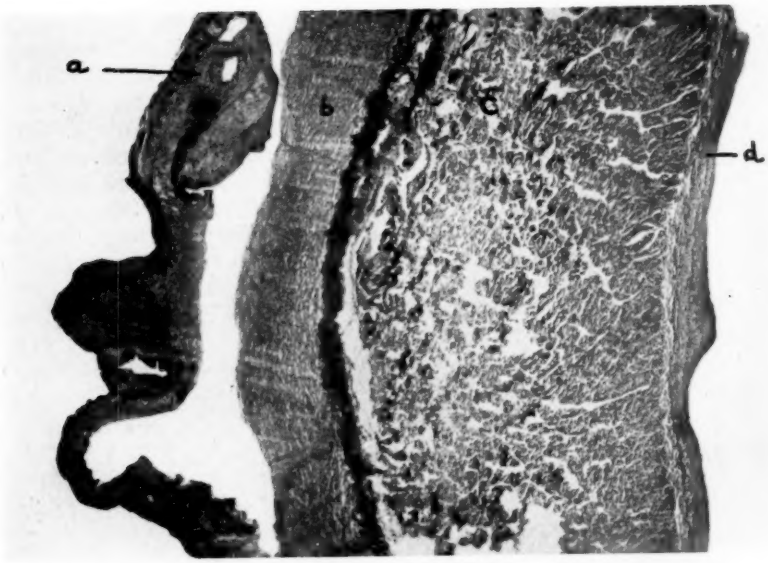

Fig. 3.—*a*. Aortic valve; *b*, aorta; *c*, myocardium; *d*, pericardium.

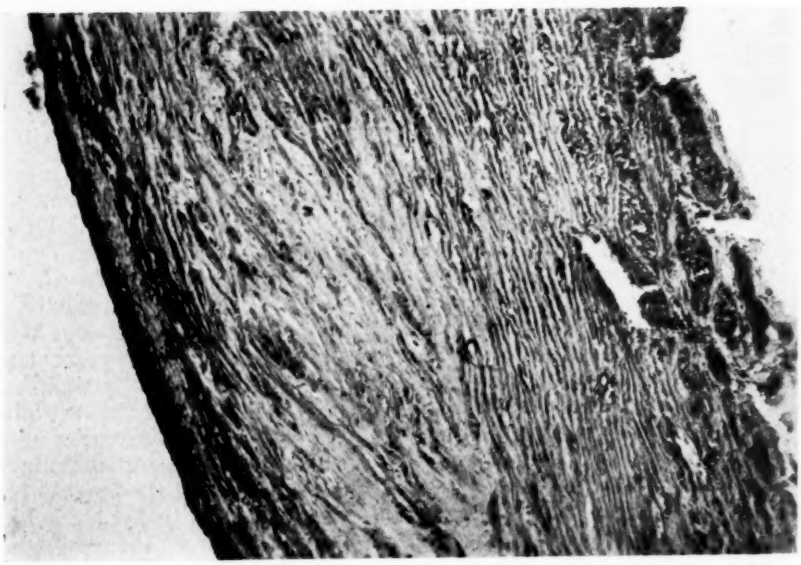

Fig. 4.

Fig. 5.

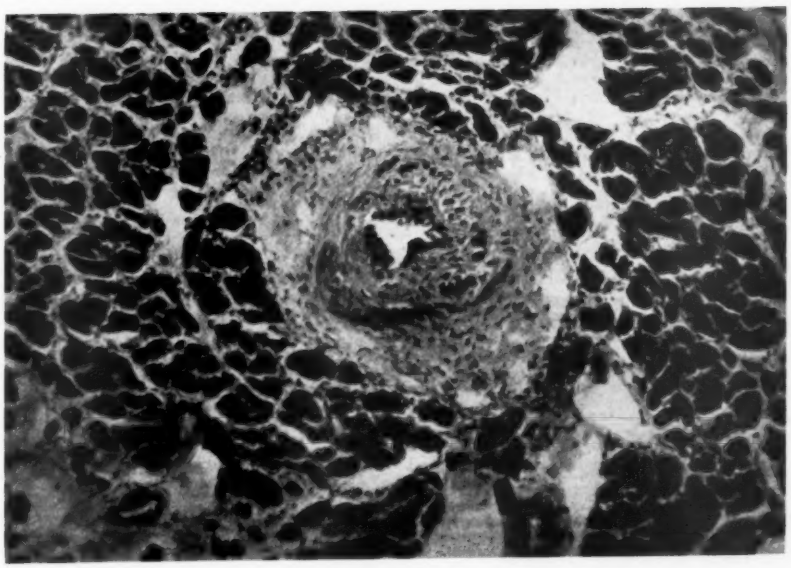

Fig. 6.

In the aortic arch there was an atheromatous plaque, partially calcified, and at its level the intima and adventitia were practically normal.

Argentic impregnation of sections of the aortic wall to demonstrate the Treponema gave negative results.

Fig. 3 shows one of the aortic valves in which chronic scleroretractile lesions were present.

In the posterior wall of the left ventricle, lesions were found that were interpreted as the result of an old, healed, myocardial infarct.

Some of the myocardial intramural vessels showed no lesions. Others, however, and particularly those in one of the sections of the papillary muscles of the left ventricle, showed lesions of chronic panvasculitis, affecting the intima, media, and adventitia. These were small vessels, with thickened walls and reduced lumina. A more detailed analysis revealed that, in some of them, there were disorganization of the endothelium, which appeared irregular and proliferated, proliferation and fibrous transformation of the intima, and thickening of the media and adventitia, with fibrosis of the latter. In others (Fig. 6), analysis revealed discrete lymphoplasmocyte and polynuclear infiltration of the adventitia, which had extended itself in the neighborhood between the myocardial fibers.

The endocardium showed slight thickening and subendocardial fibrosis.

The principal lesions in the sections which we have described may be summarized as follows:

Aorta.—Chronic endaortitis, scleroatrophic in parts, sclerohypertrophic in others. In the aortic arch, atherosclerotic lesions, partially calcified.

Chronic, destructive, scleroatrophic mesaortitis.

Marked sclerotic periaortitis, with residues of mononuclear infiltration.

Chronic, scleroretractile lesions of the sigmoid valves.

Endocardium.—Chronic fibrous endocarditis.

Myocardium.—Healed infarct in the wall of the left ventricle. Discrete, chronic, interstitial myocarditis in the remainder. Total absence of Aschoff's nodules or other specific lesions. Localized lesions of chronic panvasculitis of stenotic tendency.

DISCUSSION

Lesions of the aorta caused by congenital syphilis, especially aneurysmal dilatation, are very rare. Matusoff and White[2] stated that involvement of the heart and aorta in cases of congenital syphilis is rare; and Calvin and Nichamin[3] concluded that, although many authors believe that syphilis is the principal cause of aneurysms in children and adults, a careful study of the question does not confirm that assertion. On the other hand, Bronson and Sutherland[4] state that anatomic observations on congenitally syphilitic newborns suggest that many of the aneurysms of adolescents and young adults may be caused by congenital syphilis, and mention in this respect the observations made by Nixon[5] on a 20-year-old girl with an aneurysm of the abdominal aorta.

There has been very little mention in the literature of cases in which necropsy has been performed. Escudero[6] reported observations on two

congenitally syphilitic brothers, 4 and 6 years of age, who had a cylindrical dilatation of the aortic arch, together with aortic stenosis. Wilson and Marcy[7] appear to have been the first to verify by necropsy the existence of an aortic aneurysm caused by congenital syphilis. Navarro,[8] Acuña,[9] and Heiman[10] presented cases of aneurysm of the thoracic aorta in children, 12, 13, and 14 years of age, with congenital syphilis and positive blood Wassermann reactions. Similar observations were made by Herrera Vegas,[11] Paul,[12] and Schulte.[13] Acuña, Winocur, and Orosco,[14] at necropsy on a congenitally syphilitic girl, 6 years of age, verified the existence of multiple aneurysms of the aortic arch and thoracico-abdominal aorta, and mentioned the discovery by Muniagurria[15] of an aneurysm in a baby 8 days old. Recently, Neiman and Marks[16] presented a similar case, that of a girl 10 years of age upon whom a thorough anatomic study was made.

Our patient had all the symptoms of aortic insufficiency and an aneurysm of the ascending aorta, namely, a systolic thrill and double murmur, with maximum intensity in the second and third right intercostal spaces, dilatation of the ascending aorta, with localized expansile pulsations, etc., and this diagnosis was confirmed by necropsy.

The cause of the disease appears to us undoubtedly to have been syphilis; in fact, the Wassermann and Kahn reactions were positive, and no antecedent rheumatic fever or other infections were present. Furthermore, the microscopic study of the anatomic sections supported the clinical presumption; the lesions in the wall of the aorta were similar in every respect to those described by Neiman and Marks,[16] upon which they based their diagnosis of a syphilitic process.

Considering the absence of a history of syphilitic infection (the virginity of the patient supported this) and the evidence that the mother had syphilis (positive serologic reactions and the history of abortions), we feel that the congenital origin of the syphilitic infection cannot be doubted.

We wish to point out that the interval between the appearance of the first symptoms and the time of death was very short. This is in accordance with the observations of Cossio and Fustinoni,[17] who state that "the younger the patient, the more severe is the course of cardio-aortic syphilis when it takes the form of aortic insufficiency or aortic aneurysm."

SUMMARY

The authors comment upon observations made by clinical examination and further verified by necropsy in the case of an 18-year-old girl with intrapericardial aneurysm of the aorta caused by congenital syphilis. A review of similar cases from the literature is given. The rapid course of the malady is pointed out: only three months elapsed between the first symptoms and the time of death.

REFERENCES

1. Moore, J. E.: The Modern Treatment of Syphilis, Springfield, Ill., 1941, Charles C Thomas, p. 508.
2. Matusoff, I., and White, P. D.: Heart and Blood Vessels in Congenital Syphilis, Am. J. Dis. Child. **34**: 390, 1927.
3. Calvin, J. K., and Nichamin, S. J.: Thoracic Aortic Aneurysms in Children; Their Relation to Rheumatic Fever, Am. J. Dis. Child. **48**: 780, 1934.
4. Bronson, E., and Sutherland, G. A.: Brit. J. Child. Dis. **15**: 241, 1918.
5. Nixon, J. A.: St. Barthol. Hosp. Rep. **47**: 43, 1911. Quoted by Bronson and Sutherland.[4]
6. Escudero, P.: Arg. Med. **10**: 258, 1912.
7. Wilson, R. N.: Proc. Path. Soc. Phil. **16**: 63, 1914. Quoted by Heiman[10] and Calvin and Nichamin.[3]
8. Navarro, J. C.: Quoted by Acuña.[9]
9. Acuña, M.: Arch. Lat. Am. de Ped. **9**: 486, 1915.
10. Heiman, H.: Arch. Ped. **36**: 543, 1919.
11. Herrera Vegas, M.: Pren. Med. Arg. **8**: 1, 1921.
12. Paul, F.: Virchow's Arch. **240**: 59, 1923.
13. Schulte, K.: Ueber juvenile Mesaortitis linca, Ztschr. f. Kreislaufforsch. **22**: 753, 1930.
14. Acuña, M., Winocur, P., and Orosco, P.: Arch. argent. de pediat. **2**: 576, 1931.
15. Muniagurria: Quoted by Acuña, Winocur, and Orosco.[14]
16. Neiman, B. H., and Marks, M. B.: Productive Aortitis With Multiple Aneurysms in Child, Am. J. Dis. Child. **59**: 571, 1940.
17. Cossio, P., and Fustinoni, O.: Diagnóstico de la sífilis cardio aórtica, Día méd. **10**: 356, 1938.

Abstracts and Reviews

Selected Abstracts

Page, I. H.: The Occurrence of a Vasoconstrictor Substance in Blood During Shock Induced by Trauma, Hemorrhage and Burns. Am. J. Physiol. 139: 386, 1943.

Shock, whether elicited by tourniquets placed around the extremities, by stripping and exposing the intestines, or by hemorrhage and burns, is associated with the appearance in the plasma of a substance which causes vasoconstriction in rabbits' ears perfused with either calcium-free Ringer's solution or plasma. It does not originate in the kidneys or adrenal glands, nor does destruction of the spinal cord or renal denervation prevent its appearance. Evidence gathered from application of a method depending on "fatiguing" the vascular musculature suggests, if the validity of the method is acceptable, that the vasoconstrictor action of plasma from burned, bled, and shocked dogs is caused by identical or very similar substances. Furthermore, it differs from the vasoconstrictors present in hypertensive's (human and canine) plasma and in serum (human and canine). None of these vasoconstrictors seem to be histamine. This belief is confirmed by experiments on isolated intestine which show that serum causes marked contraction while plasma from burned or shocked dogs causes none.

AUTHOR.

Leeds, S. E.: The Effects of Occlusion of Experimental Chronic Patent Ductus Arteriosus on the Cardiac Output, Pulse and Blood Pressure of Dogs. Am. J. Physiol. 139: 451, 1943.

A condition similar to patent ductus botalli was produced in dogs by lateral anastomosis of the aorta to the left pulmonary artery and by end-to-side anastomosis of the left subclavian to the left pulmonary artery.

Studies were made of both the immediate and late effects of production of the experimental ductus arteriosus on the cardiac output, pulse, and content of oxygen in the blood.

A study was also made of the immediate effects of occlusion of chronic experimental ductus arteriosus on the pulse, systemic blood pressure and that of the pulmonary artery and the cardiac output.

In the experiments of long standing the flow of blood through the experimental ductus arteriosus was calculated.

The significance of the findings as related to surgical ligation of patent ductus botalli in human patients is suggested.

AUTHOR.

Bozler, E.: Tonus Changes in Cardiac Muscle and Their Significance for the Initiation of Impulses. Am. J. Physiol. 139: 477, 1943.

The after-potentials of cardiac muscle previously described are accompanied by changes in "tonus." In fresh muscle the tension drops slightly below the previous level corresponding to the positive after-potential observed under the same conditions. This phenomenon is significant because it indicates the presence of a

tonic contraction in "resting" muscle. After treatment with an excess of calcium ions the responses are followed by oscillatory changes in tension.

The tonus changes and the local potentials are probably manifestations of a more fundamental process, a fluctuation in resting metabolism. The mechanical changes are weak and hardly play any role as such. Their chief interest lies in their relation to the automaticity and rhythmicity of the muscle. It may be assumed that an increase in metabolism causes a rise in tonus and a decreased surface polarization. The decrease in polarization in turn may be considered as the last link in the chain of processes leading to the discharge of an impulse.

AUTHOR.

Rosenblueth, A., and Del Pozo, E. C.: The Changes of Impedance of the Turtle's Ventricular Muscle During Contraction. Am. J. Physiol. **139,** 514, 1943.

The changes of electrical impedance during the activity of the turtle's ventricle were measured by means of an alternating current bridge and recorded from a cathode-ray oscillograph.

The impedance to alternating currents of 30 to 10,000 cycles per second and of 0.04 to 0.06 ma. increases during activity. The increase begins approximately at the same time as contraction, but it outlasts the mechanical events. There is no parallelism between the impedogram and the electrogram. Brief electrical and mechanical responses involve a brief impedance variation.

Upon repetitive stimulation a long enduring impedance change may ensue.

The early part of the ventricular electrogram is not attended by any striking change of impedance.

AUTHORS.

Kosupkin, J. M., and Olmsted, J. M. D.: Slowing of the Heart as a Conditioned Reflex in the Rabbit. Am. J. Physiol. **139:** 550, 1943.

It is possible so to condition a rabbit as to slow its heart rate by using inhalation of ammonia as the unconditioned stimulus and the ringing of a bell as the conditioned stimulus.

AUTHORS.

Nahum, L. H., Hamilton, W. F., and Hoff, H. E.: The Injury Current in the Electrocardiogram. Am. J. Physiol. **139:** 202, 1943.

Injury to the right ventricle causes an upward displacement of the diastolic base line in the three standard leads of the electrocardiogram. Injury to the left ventricle produces a downward displacement of the diastolic base line.

During systole there is a return of the string to the isopotential level which constitutes the S-T segment.

In reality, therefore, elevated S-T segments must be interpreted as due to an injury potential resulting from left ventricular damage, which produces in the electrocardiogram a downward displacement of the diastolic base line.

Depressed S-T segments must be interpreted as due to an injury potential resulting from right ventricular damage, which produces in the electrocardiogram an upward displacement of the diastolic base line.

AUTHORS.

Rosenblueth, A., Daughaday, W., and Bond, D. D.: The Electrogram of the Turtle's Heart. Am. J. Physiol. **139:** 464, 1943.

Evidence is presented which indicates that the electric phenomena recorded from leads on an intact and an injured region of the turtle's ventricle are due to

changes which occur in the intact, not the injured part of the muscle. This record may be called monotopic, to avoid the use of other ambiguous terms. This electrogram exhibits several components which may vary independently. The significance of some of these components is discussed.

The records with leads from intact to intact tissue are influenced by the position of the leads with respect to the stimulated region. They may also be modified in the course of a series of responses. These records may be called ditopic, since they represent the algebraic summation of two monotopic records.

The electric and the mechanical phenomena of the ventricle are largely independent.

AUTHORS.

Garvin, C. F.: Gallop Rhythm—Incidence and the Influence of Age, Race, and Sex. Am. J. M. Sc. 205: 814, 1943.

Of 790 consecutive, adult, autopsied patients dead of heart disease, 199 (25.2 per cent) had had gallop rhythm due either to auricular contraction or a third heart sound. Gallop rhythm occurred most frequently in hypertensive heart disease and coronary artery disease; one out of every three patients had this type of rhythm. Cor pulmonale was associated with gallop rhythm in about one case in five. Only one of ten patients who died of rheumatic heart disease or syphilitic heart disease had gallop rhythm.

The average age of death of 93 patients with hypertensive heart disease and gallop rhythm was 49.5 years, of 171 patients with hypertensive heart disease and no gallop rhythm, 58.8 years. Patients with coronary artery disease and gallop rhythm (55) averaged 57.3 years at death; 122 patients with coronary heart disease and no gallop rhythm averaged 64.4 years. Both of these differences seem to be statistically highly significant. Even if patients with auricular fibrillation are excluded (such patients rarely have gallop rhythm and are apt to be older), it still appears that the average age at death of cardiac patients with gallop rhythm is less than the average age of cardiac patients without gallop rhythm.

When patients with hypertensive and/or coronary heart disease were grouped together, it was found that, of 326 white patients, 100 (30.7 per cent) had a gallop rhythm, while of the 115 colored patients, 48 (41.7 per cent) had a gallop rhythm. This seems to indicate that colored patients with fatal hypertensive heart disease and/or coronary heart disease, show a higher incidence of gallop rhythm than white patients. It is thought that this is really a manifestation of the influence of age, for the average age at death of the colored patients was less than that of the white patients.

No association between gallop rhythm and sex was demonstrable.

AUTHOR.

Mazer, M., and Reisinger, J. A.: Criteria for Differentiating Deep Q_3 Electrocardiograms From Normal and Cardiac Subjects. Am. J. M. Sc. 206: 48, 1943.

A series of 102 electrocardiograms with significantly deep Q_3 waves has been analyzed. Criteria have been suggested to aid in differentiating those from normal and diseased hearts.

AUTHORS.

Evans, W., and Hunter, A.: Chest Lead CR_7 in Cardiac Infarction. Brit. Heart J. 5: 73, 1943.

A new chest lead, CR_7 is described and has been tested in the differential diagnosis of cardiac infarction.

The lead proved to have a limited value in identifying posterior infarction, but it was superior to the limb leads. The authors' experience has emphasized the importance of T_2 in posterior infarction, for in 30 out of 32 patients it supplied the evidence necessary for the diagnosis. In contrast, T_2 in anterior infarction was less reliable, and T in CR_7 was often its superior, although inferior to T in R_4.

CR_7 had greatest value in distinguishing between the T_3 and T_3 inversion of posterior infarction and similar changes found in heart failure from emphysema, in pericardial disease, in congenital heart disease, and occasionally in healthy subjects. This new chest lead also helped in the diagnosis of hypertension and aortic valvular disease when complicated by anterior cardiac infarction.

AUTHORS.

Sharpey-Schafer, E. P.: Potassium Effects on the Electrocardiogram of Thyroid Deficiency. Brit. Heart J. 5: 85, 1943.

The flat T wave of thyroid deficiency became upright after potassium. Inverted T waves also became upright, a response which is similar to that in preponderance of a ventricle and unlike that of myocardial infarction. A case of Addison's anemia showed accentuation of S-T depression.

AUTHOR.

Sharpey-Schafer, E. P.: Potassium Effects on T-wave Inversion in Myocardial Infarction and Preponderance of a Ventricle. Brit. M. J. 5: 80, 1943.

T-wave inversion due to myocardial infarction is further inverted by raising the serum potassium, while T-wave inversion due to preponderance of a ventricle becomes upright after potassium.

The method is useful in analysis of difficult electrocardiograms. It is suggested that T inversion in ventricular preponderance is an S-T change, not a T-wave change.

AUTHOR.

Shapiro, M. J., and Keys, A.: The Prognosis of Untreated Patent Ductus Arteriosus and the Results of Surgical Intervention: A Clinical Series of 50 Cases and an Analysis of 139 Operations. Am. J. M. Sc. 206: 174, 1943.

Diagnosis of patent ductus arteriosus can be made with great certainty, and complications making surgical ligation unadvisable are readily recognized.

The great majority of patients with this defect suffer no serious disability or restriction of activity during most of their lives, but their life expectation is greatly shortened by the continued presence of the defect.

Experience to date shows that ligation of the uninfected ductus can be made with a mortality of less than 10 per cent.

Ligation of the ductus in the presence of subacute bacterial endarteritis offers an even chance of survival in the face of practically certain death without ligation.

The danger of development of subacute bacterial endarteritis after successful ligation cannot properly be estimated as yet.

Six case histories are cited which illustrate opposing arguments for and against ligation.

An analysis is presented of the results of 140 operations to ligate the ductus.

It is concluded that the majority of patients with patency of the ductus arteriosus should be sent to surgery for ligation after careful clinical studies have been made on them.

Ligation should be attempted immediately if subacute bacterial endarteritis develops.

Ten patients with uninfected patent ductus arteriosus have been operated upon by Dr. O. N. Wangensteen at the University of Minnesota Hospital, the last eight cases with complete success. As far as is known, in none of them has there been a recurrence of signs indicating recanalization.

AUTHORS.

Bain, C. W. C., and Parkinson, J.: Common Aorto-Pulmonary Trunk: A Rare Congenital Defect. Brit. Heart J. 5: 97, 1943.

A common aorto-pulmonary trunk, as an isolated gross congenital malformation, was found at death in a man of 18 years, who had always been cyanosed and breathless. Electrocardiograms, radiographs, and pathologic details are recorded. The malformation cannot be classified as persistent truncus arteriosus, because there was neither a defect of the interventricular septum, nor any abnormality of the aortic and pulmonary valves.

AUTHORS.

Baker, L. A., Sprague, H. B., and White, P. D.: The Clinical Significance of Loud Aortic and Apical Systolic Heart Murmurs With Diastolic Murmurs. Am. J. M. Sc. 206: 31, 1943.

Determination of the status of 187 private patients who showed loud systolic murmurs, best heard at either the apex or aortic area, but no diastolic murmurs, ten to twenty-one years after they were first examined, resulting in finding that 155 (82.5 per cent) were dead. Death was due to heart disease in 122 (78.7 per cent).

Seventy-four (47.7 per cent) of all deaths occurred within a year after the first examination, while 110 (70.8 per cent) of the deaths occurred within three years.

The outlook for the younger patients with rheumatic heart disease was somewhat better than for those with heart disease of "degenerative" or uncertain etiology. In spite of the high death rate, only 24 of the 155 deaths occurred under the age of 50 years. The death rate was lower among females for the ten-year period but equaled that of the males by the end of fifteen years. Of the deaths among those with rheumatic heart disease, 24 per cent were due to subacute bacterial endocarditis. Those with larger hearts had a higher mortality. Despite these prognostic trends, however, it is impossible to predict with any high degree of assurance the course of any particular case.

An interesting and important observation is that some cases, originally diagnosed as having mitral regurgitation because of a loud apical systolic murmur, were later found to have aortic stenosis, which, in the course of ten to fifteen years, tended to precipitate abrupt left ventricular failure (acute pulmonary edema). The clue to these cases lies in the fact that the loud, somewhat harsh, systolic murmur heard at the apex is also heard at the aortic valve area, although perhaps less loudly. The murmur is primarily an aortic systolic murmur transmitted to the apex as well as into the neck vessels; a mitral regurgitant murmur is often heard at the lung bases (and in the left axilla) but not at the aortic valve area.

It is evident that loud systolic murmurs at the cardiac apex or aortic valve area are clinically important even in the absence of diastolic murmurs and a well-marked cardiac enlargement.

AUTHORS.

Bloom, F.: Structure and Histogenesis of Tumors of the Aortic Bodies in Dogs. Arch. Path. **36**: 1, 1943.

Two similar tumors occurring spontaneously in the region at the base of the heart in dogs are reported. They had essentially the same anatomic location and histologic characteristics as the aortic bodies. It is considered, therefore, from the morphologic evidence, that the tumors originated from these structures. The aortic bodies are homologous with the carotid body, and the specific cells are neuroepithelial sensory cells that function as chemoreceptors. In view of the complex nature of the chemoreceptors, it is suggested that neoplasms of these structures be designated as tumors of the aortic bodies and tumors of the carotid body.

AUTHOR.

Peel, A. A. F.: Anginal Pain in Myxedema. Brit. Heart J. **5**: 89, 1943.

Several types of anginal pain may occur in myxedema.

Angina of effort occurs frequently when there is independent heart disease and occasionally with an uncomplicated myxedema heart. In the presence of independent heart disease, angina is sometimes aggravated, sometimes alleviated, and sometimes unaffected by thyroid therapy. For many patients there is an optimum dose, up to which improvement results, but beyond which pain is aggravated; the optimum dose is often sufficient to procure great improvement in the patient's general condition and to permit a fair amount of activity; in favorable cases the angina is abolished on the optimum dosage. When a patient with myxedema and independent heart disease suddenly develops effort angina during thyroid treatment and apart from an increase in dosage, the cause is frequently a small coronary occlusion; caution suggests that the dose should be temporarily reduced or discontinued; but once the stage of convalescence has been reached, resumption of therapy does not aggravate the pain, and there seems to be no reason for withholding the benefits of the drug.

A constant pain or ache, aggravated during effort, and tending to be associated with attacks of collapse, occurs in some cases of mild or subclinical myxedema; it is referred to as the "abortive myxedema heart of Zondek." It improves with thyroid therapy, but in these cases, too, there may be an optimum dose. If unrecognized and untreated, the patients may develop a clinical myxedema or a typical angina of effort.

Spasmodic angina occurred in two cases. Both may have had very early hypertension, but neither had any obvious or advanced complicating heart disease. In one, the possibility of hypoglycemia was considered; the attacks ceased on treatment with thyroid and a dose of glucose at bedtime. In the other, there was a complicating anemia; the attacks ceased when this was treated and before any thyroid was given. In neither case did thyroid aggravate the spasmodic angina nor did it produce an effort angina.

The occurrence of anginal pain in a myxedematous patient does not contraindicate the cautious use of thyroid; only when pain develops in response to an increased dosage is there justification for blaming the drug, and even then it may be tolerated at a later date. AUTHOR.

Lange, K.: A Recording Sphygmotonograph: A Machine for the Continuous Recording of Systolic and Diastolic Arterial Pressure in Man. Ann. Int. Med **18**: 367, 1943.

A machine is described which automatically takes continuous records of the systolic as well as diastolic blood pressure of man.

The principle and the detailed construction are shown and the mechanical arrangements and working conditions discussed. The inertia of the machine is shown and the meaning of the obtained tracings are discussed.

A simple mechanical contact device is not satisfactory for registering the diastolic pressure since it is dependent on the magnitude of the oscillations instead of on the steepness of the ascending branch. A heated wire system (balometer) is used to transform the puffs of air into electric currents.

The steepness of the ascending branch of the diastolic oscillation is an exact criterion for the diastolic pressure.

The accuracy of the sphygmotonograph was proved by comparisons with the auscultatory method in 109 patients. The average difference for the systolic pressure was 0.06 mm. Hg, for the diastolic pressure 4.0 mm. Hg.

Records taken from both arms of the same patient with two machines are identical.

Taking uninterrupted records for a period of thirty minutes, with partial arrest of the circulation in the limb concerned, does not produce any detrimental effect on the vessels, nerves, or muscles.

The partial arrest of circulation and the pressure on the limb does not produce changes in the blood pressure.

Comparative measurements with the Korotkov method, using a recording microphone instead of the stethoscope, show the accuracy of the syphgmotonograph.

Many normal persons show Mayer-Traube-Hering waves of a wave length of about 30 seconds and a height up to 12 mm. Hg in size, under excitement and impaired breathing conditions.

Even slight mental work or excitement may cause a considerable increase in diastolic and systolic blood pressure, especially in individuals in the very beginning of hypertension.

AUTHOR.

Fishback, H. R., Dutra, F. E., and MacCamy, E. T.: The Production of Chronic Hypertension in Dogs by Progressive Ligation of Arteries Supplying the Head. J. Lab. & Clin. Med. **28**: 1187, 1943.

Chronic hypertension has been produced in dogs by ligation, in series, of the arteries supplying the head.

Removal or manipulation in situ of the carotid sinuses alone has no prolonged effect on the blood pressure of dogs.

AUTHORS.

Warthin, T. A., and Thomas, C. B.: Studies in Experimental Hypertension. I. Phenol Red Excretion and Renal Blood Flow in Hypertension of Renal Origin. Bull. Johns Hopkins Hosp. **72**: 203, 1943.

Arterial hypertension was induced in five dogs with single explanted kidneys by partial occlusion of the renal artery. Two dogs died in uremia, one and six weeks, respectively, after application of the clamps. Three dogs survived and were killed, three, seven, and eleven months, respectively, after the clamps were applied.

Studies of the rate of urinary excretion of phenol red, and of the renal blood flow through the extraction of phenol red by the kidney, were made in these animals before and after the renal arteries were constricted.

Immediately before or coincident with the onset of hypertension, a reduction in renal blood flow and phenol red excretion occurred. After three to four weeks, the renal blood flow returned to the control levels, but the hypertension persisted. In four to seven weeks, the phenol red excretion likewise returned to normal values.

These experiments indicate that chronic experimental hypertension of renal origin may persist after the renal blood flow has returned to normal.

Pentobarbital anesthesia in these animals produced a fall in blood pressure and renal blood flow both before and after hypertension was induced.

AUTHORS.

Alpert, L. K., and Thomas, C. B.: Studies in Experimental Hypertension. II. The Effect of Dietary Protein on the Urea Clearance and Arterial Blood Pressure in Chronic Hypertension. Bull. Johns Hopkins Hosp. 72: 274, 1943.

Determinations of the clearance of urea during periods of varying protein intake were made in five dogs. Two of the dogs had chronic experimental hypertension of renal origin, two had chronic neurogenic hypertension, and one had normal blood pressure.

The urea clearance values were normal in all of the animals during periods of low protein intake and showed pronounced elevations when the dogs were fed diets high in protein.

Since variations in urea clearance are associated with parallel changes in renal blood flow, these results suggest that there may be no impairment of renal blood flow in dogs with chronic experimental hypertension.

The variations in arterial pressure during the experimental diets were not great and could not be correlated with the changes in protein intake or urea clearance.

AUTHORS

Alpert, L. K., and Lilienthal, J. L., Jr.: Studies in Experimental Hypertension. III. The Effect of Dietary Protein on the Clearances of Diodrast and Insulin by the Kidney in Chronic Hypertension. Bull. Johns Hopkins Hosp. 72: 286, 1943.

Simultaneous determinations of the renal clearances of diodrast, inulin, and urea were made in six dogs during periods of low and high protein intake. Two of the dogs had chronic hypertension of renal origin, had two chronic neurogenic hypertension, and two had normal blood pressures.

The clearance values of all the substances under consideration were much greater during the periods of high protein intake than during the low ones. The inulin and urea clearances were increased to a relatively greater degree than were the diodrast clearances.

No qualitative differences were noted in the response of the normal renal hypertensive and neurogenic hypertensive dogs to the changes in diet.

No significant anatomical abnormalities were found in the blood vessels, kidneys, or other organs of the dogs at post-mortem examination.

It is concluded that the blood flow and functional activities of the kidneys of dogs with chronic experimental hypertension may be unimpaired, and may react to the stimulus of increased dietary protein in a manner which is indistinguishable from the normal.

AUTHORS.

Talbott, J. H., Castleman, B., Smithwick, R. H., Melville, R. S., and Pecora, L. J.: Renal Biopsy Studies Correlated With Renal Clearance Observations in Hypertensive Patients Treated by Radical Sympathectomy. J. Clin. Investigation 72: 387, 1943.

Renal clearance studies performed on twenty patients with essential hypertension showed a significant correlation with the microscopic appearance of their respective renal tissues which were removed for biopsy at the time of sympathec-

tomy, i.e., the more severe the renal vascular disease, the more reduced were the glomerular filtration rate and the renal blood flow. In the cases with Grade 0 and I renal vascular disease, the renal clearance observations were either normal or only very slightly reduced. Only in Grade IV renal vascular disease was renal blood flow seriously reduced.

The filtration fraction was normal in seven out of eight cases in biopsy groups 0, I, and II. It was increased in six of eleven cases in biopsy groups III and IV. These findings indicate that constriction of the efferent glomerular arterioles was not present in the early stages of renal vascular disease.

Bilateral radical lumbodorsal splanchnicectomy had relatively little effect on renal clearance, when measured in the horizontal position. Although glomerular filtration was reduced in the immediate postoperative peroid about 20 per cent, within a year it returned to and continued to maintain its preoperative level. Renal plasma flow was essentially unchanged.

AUTHORS.

Corcoran, A. C., and Page, I. H.: Effects of Hypotension Due to Hemorrhage and of Blood Transfusion on Renal Function in Dogs. J. Exper. Med. **78**: 205, 1943.

Renal blood flow is decreased by hypotension due to bleeding, and glomerular filtration rate is disproportionately decreased. After a first forty-minute stage of hypotension at about 60 mm. Hg, infusion of blood with consequent restoration of the general blood volume and arterial pressure usually results in a return to normal of renal blood flow and function although renal blood flow subsequently tends to decrease. The restoration of renal blood flow and function is associated with an increase of urine flow above the control level.

Diodrast clearance loses its value as a measure of renal plasma flow (a) during severe or prolonged hypotension, and (b) immediately after restoration of arterial pressure by infusion after a first stage of hypotension. In the former case (a), it is decreased in consequence of decreased renal extraction of diodrast flow through nephrons whose vascular resistance is low; (b) the disparity after transfusion is due to excretion of diodrast accumulated in the kidney tubules and, presumably, in the interstitial fluid during hypotension. The presence of diodrast and inulin in the renal interstitial fluid explains the addition of these substances to renal venous blood observed in some of these experiments. The shifting equilibrium of diodrast between renal plasma and interstitial fluid may explain some of the instances of low diodrast extraction observed in these experiments during transfusion after hypotension, and may explain also the incomplete renal extraction of diodrast under normal conditions.

Dogs with denervated kidneys respond to blood transfusion and restoration of arterial pressure by a disproportionately slow and incomplete return towards normal of renal clearance and, presumably, of renal blood flow. On the basis of these facts, it is suggested that high spinal anesthesia may interfere with recovery of renal circulation in cases of shock treated by transfusion.

Profound or prolonged and repeated hypotension due to bleeding decreases the ability of normal and denervated kidneys of intact and anesthetized dogs to respond to transfusion and the restoration of arterial pressure by proportionately increased clearance and plasma flow, apparently because of renal vasoconstriction due to the release of humorally circulating vasoconstrictor substances.

AUTHORS.

Jahsman, W. E., Durham, R. H., and Dallis, N. P.: Recognition of Incipient Thromboangiitis Obliterans in Young Draftees. Ann. Int. Med. **18**: 164, 1943.

Thromboangiitis obliterans occurs in young draftees and should not be overlooked because of possible long-continued disability compensation if such draftees are accepted for active service.

Incipient stages of the disease may be recognized from the nail fold capillary picture described, together with a modification of the Gibbon and Landis dermatherm study.

In these early stages there is diminution in vasodilatation of mild to moderate degree in at least one lower extremity. In the four cases reported, the maximum temperature rise in the most involved extremity, after immersion of a forearm in water at 110° to 114° F., was from 2.5° to 4.8° C. below the accepted normal of 32° to 33° C. Later, with more actual occlusion, there is constant coldness of the skin as in arteriosclerosis obliterans and little or no temperature rise on exposure to heat.

Two of the patients did not show as low a level of skin temperature as is usually seen after exposure of the feet and legs in a cool room for thirty minutes. It might be speculated that with a more active inflammatory process in the vessels in this stage of the disease there might be less vasoconstricting ability. A more likely explanation is the individual differences that are bound to be found in the way of sensitiveness to cold, even with an early disease process present.

Having diagnosed the disease early, it should be possible to keep these young men reasonably free from symptoms and prevent complications by teaching them more moderate habits of living and meticulous care of the feet.

AUTHORS.

Blakemore, A. H., and Lord, J. W., Jr.: Restoration of Blood Flow in Damaged Arteries: Further Studies on a Nonsuture Method of Blood Vessel Anastomosis. Ann. Surg. **117:** 481, 1943.

The problem of blood vessel anastomosis deserves important consideration in this war because advances in the control of serious infection and the possible use of anticoagulants afford, for the first time in the history of wars, a basis for success; the outstanding cause of the loss of limbs in this war will be damage to the blood supply.

Vitallium is presented as a nonirritating alloy suitable as a prosthesis for a vein graft bridging an artery or vein defect in a nonsuture method of vessel anastomosis using a single or double tube technique.

Carefully controlled experiments on dogs are presented, demonstrating that sulfathiazole by mouth contributed greatly to the success of delayed anastomoses of severed vessels in contaminated wounds. Using sulfanilamide in alternate wounds in a series of 77 anastomoses, it was noted to be of moderate but definite value.

The nonsuture method was shown to be highly successful in anastomosing the small femoral arteries of dogs, even in contaminated wounds twenty-four hours after section of the artery, and without the use of anticoagulants.

It is assumed that vein graft anastomoses of the severed primary artery in the war-wounded will prevent the loss of the extremity by gangrene if the anastomosis remained patent beyond the posttraumatic edema, up to fourteen days.

Experiments are presented showing that veins taken from one dog may continue to function in another when used as transplants to bridge vessel defects; for example, the successful reimplantation of limbs twenty-four hours after their removal. These experiments afford a prospect for the use of preserved veins as grafts for bridging vessel defects in the war-wounded as an alternate to the use of homoplastic transplants.

AUTHORS.

Bremer, J. L.: Congenital Aneurysms of the Cerebral Arteries: An Embryologic Study. Arch. Path. **35:** 819, 1943.

The cerebral arteries are evolved from a capillary plexus arising from the earliest branch of the primitive aortic arch, which runs along the under side of the brain. From the rostral end of the plexus, branches go in front of the bulging

hemisphere and over its lateral surface, becoming the anterior and middle cerebral arteries. Another part of the plexus becomes the posterior cerebral artery, covering the diencephalon and midbrain. The anterior artery gains the mesial surface of the frontal lobe; the posterior supplies the similar surface of the posterior lobes that their expansion covers in the diencephalon. All cerebral arteries approach from the lesser curvature of the expanding hemisphere, and the interstitial growth of the latter during fetal life rapidly spreads the forks of their branches. Other growth changes have the same action. If these forks lack the media, the rapid spread may produce local aneurysms.

From all the cerebral arteries and from the main basal trunk, smaller branches dip into the brain substance and also supply the meninges. These also form plexuses. Proximal members of such plexuses may enlarge while their distal continuations degenerate and may thus become aneurysmal pouches from the main vessels. Both types may be true congenital aneurysms.

AUTHOR.

Rottino, A., and Poppiti, R.: Intimal Changes in Medial Degeneration of the Aorta. Arch. Path. **36**: 201, 1943.

A report of a case of severe medial degeneration of the aorta with a tree bark type of intima is presented. Syphilitic mesaortitis and endoarteritis obliterans of the vasa vasorum were not present. It is contended that the intimal lesion in this case is not syphilitic and is secondary to mural weakness resulting from medial degeneration.

Brief mention is made of the incidence of intimal lesions in cases of medial degeneration.

AUTHORS.

Blalock, A.: Effects of Lowering Temperature of an Injured Extremity to Which a Tourniquet Has Been Applied. Arch. Surg. **46**: 167, 1943.

The results of the experiments reported indicate that the use of a tourniquet on an injured extremity should be avoided whenever possible, but that, if some form of constriction is necessary, the temperature of the distal ischemic and anemic part should, if possible, be lowered by artificial means.

AUTHOR.

Essex, H. E., Herrick, J. F., Baldes, E. J., and Mann, F. C.: Observations on the Circulation in the Hind Limbs of a Dog Ten Years Following Left Lumbar Sympathetic Ganglionectomy. Am. J. Physiol. **139**: 351, 1943.

Observations have been made on the blood flow in the femoral arteries of a dog at intervals over a period of ten years and two months. Blood flow was measured in both femoral arteries simultaneously under infiltration anesthesia before sympathetic ganglionectomy, and fifteen days, ten months twenty-five days, nine years two months, and ten years two months, after sympathectomy. Whereas the flow was twice as great in the left or sympathectomized limb as it was in the right or control limb fifteen days, and also ten months and twenty-five days after sympathectomy, the flow was almost the same in the two limbs nine, and also ten years after sympathectomy.

That the vessels of the sympathectomized leg were profoundly hypersensitive to epinephrine more than nine and ten years after sympathectomy was shown by a small injection of epinephrine, which caused such a marked constriction of the vessels of the sympathectomized side that the flow was zero for at least two minutes. The flow on the control side taken at the same time was only slightly altered.

Simultaneous plethysmographic records of the two hind feet further confirmed the observations on blood flow, since there was a transient decrease of the volume of the innervated foot but a very prolonged decrease of that of the denervated foot in response to small doses of epinephrine.

Histologic examination of a toe from each hind foot showed that the arterioles of the left or sympathectomized foot had undergone hypertrophy which was confined to the muscularis coat of the vessels. The vessels of the control side did not show hypertrophy.

AUTHORS.

Meneely, G. R., and Kaltreider, N. L.: A Study of the Volume of the Blood in Congestive Heart Failure. Relation to Other Measurements in Fifteen Patients. J. Clin. Investigation 22: 521, 1943.

In fifteen patients with severe congestive heart failure, the blood volume, arterial and venous blood pressure, arm-to-tongue circulation time, vital capacity, arterial and venous oxygen and carbon dioxide content and oxygen combining power, volume of packed red cells, plasma carbon dioxide combining power, and plasma total proteins were measured and are reported.

The blood volume was increased in all cases, and, in most, the increase was substantial.

There was great variability in the increase and in the degree to which the plasma and the cells contributed to the increase, and no statistically significant difference was observed between the increase in cell and plasma volume.

There was no simple correlation between the total blood volume and the other measurements made, nor between the venous pressure and the circulation time.

A negative correlation of moderate significance was found between the venous pressure and the plasma volume.

The logarithm of the circulation time bore a linear relation to the ratio between the transverse diameter of the heart and the internal diameter of the chest in eight cases where roentgenograms of the chest were taken.

The venous hematocrit and hemoglobin gave little indication of the actual volume of circulating cells.

There was a highly significant correlation between the degree of anoxemia measured by Lundsgaard's "capillary unsaturation" and the increase in cell volume.

In three patients who improved, all measurements tended toward normal, the plasma volume decreasing more than the cell volume. In the patients who grew worse, the reverse was the case.

AUTHORS.

Shipley, R. E., Gregg, D. E., and Schroeder, E. F.: An Experimental Study of Flow Patterns in Various Peripheral Arteries. Am. J. Physiol. 138: 718, 1943.

Flow patterns (and simultaneous intra-arterial pressure curves) have been optically recorded with an improved orifice-type flow meter in the renal, hepatic, superior mesenteric, femoral, axillary and common carotid arteries of dogs to which have been administered only anesthetic and anticoagulant.

A flow pattern may be characteristically distinctive of a given artery and its bed, but flow patterns in heteronymous arteries are found to exhibit wide variations in magnitude, timing, direction, and rate of flow, and in similarity of contour to their respective pressure pulses. Back flow components have been consistently found to exist in the femoral and axillary arterial flow patterns, frequently found in the common carotid patterns, while the renal, hepatic, and superior mesenteric have exhibited only forward flow.

A study has been made revealing the probable determinants of, and their interrelated influences upon, the phasic rate of inflow to a bed (flow pattern) under the above and other physiologic conditions.

Although the above analysis does not lend itself to a quantitative evaluation of the static and dynamic factors which initiate and moderate the phasic rate of inflow to a bed, it constitutes a basis for a qualitative evaluation of differences among, and changes in, flow patterns, recorded in the same or different arteries under various physiologic conditions.

AUTHORS.

Pritchard, W. H., Gregg, D. E., Shipley, R. E., and Weisberger, A. S.: A Study of Flow and Pattern Responses in Peripheral Arteries to the Injection of Vasomotor Drugs. Am. J. Physiol. 138: 731, 1943.

Optically recorded flow patterns (with an improved orifice type meter) together with the coexisting pressure pulses in the superior mesenteric, hepatic, renal, common carotid, axillary, and femoral arteries of anesthetized dogs are presented. The effects of intra-arterial and intravenous administration of vasodilator and constrictor drugs on the flow and pressure curves are shown. Following the system of analysis previously described, several series of curves have been examined with reference to changes in mean flow; relationship of mean flow to mean pressure; similarity of contour between patterns and pressure pulses; volume of pulsatile deviation from the mean rate of flow (dynamic volume-elastic properties of the vascular tree), and the vasomotor state of the bed (dilatation or constriction).

The generally accepted vasomotor responses to so-called dilator and constrictor drugs given intra-arterially were observed. However, in some records, and especially in those obtained following intravenous drug administration, changes in the vasomotor state of the bed could not be determined because of the overlapping of central and peripheral drug effects.

The dynamic volume-elastic component is reduced, except in the common carotid artery, by vasoconstrictor drugs given intra-arterially, while vasodilators usually increase this fraction during most of the period of drug action.

The injection of constrictor drugs, either intravenously or intra-arterially, may cause the appearance or augmentation of back flow in the patterns of all peripheral arteries so far studied. Dilators may introduce backflow in the common carotid pattern and greatly augment that pre-existing in the common carotid, axillary, and femoral patterns.

The interrelationship of the determinants associated with vasomotor drug effects is considered and discussed.

AUTHORS.

Hiatt, E. P., and Garrey, W. E.: Drug Actions of the Spontaneously Beating Turtle Ventricle Indicating Lack of Innervation. Am. J. Physiol. 138: 758, 1943.

Isolated strips of the ventricle of the turtle heart will beat spontaneously and regularly if bathed in a well-oxygenated physiologic saline solution containing potassium and calcium in equivalent molar concentration but having less potassium than turtle serum.

These ventricular strips do not show inhibition either of impulse initiation or contractility when treated with acetylcholine (plus eserine) or pilocarpine in concentration far in excess of those required to inhibit the auricle and the frog ventricle. This confirms previous work indicating that the turtle ventricle lacks a vagus nerve supply.

Adrenalin and ephedrine cause a small increase in the amplitude of the contractions of ventricular strips but the effect is quite small compared with the effect on the auricle and on the frog ventricle. It is suggested that this indicates a lack of sympathetic nerve supply.

A small excess of potassium, which has little effect on the auricle or the frog ventricle, causes cessation of the beat of fresh turtle ventricle strips. The effect is not on the contractile process. The sensitivity of these strips of turtle ventricle to potassium decreases with time after excision.

Calcium excess causes an increase in the amplitude of both auricular and ventricular contractions.

It is indicated that acetylcholine, pilocarpine, adrenalin, and ephedrine have their principal effects on the heart muscle only through the receptor substance which accompanies innervation. Adrenalin and ephedrine have a slight stimulating action on the aneuric myocardial tissue. Potassium and calcium appear to have a definite action directly on the myocardial cells lacking the receptor substance.

AUTHORS.

Leathem, J. H., and Drill, V. A.: The Effect of Diethylstilbestrol on the Blood Pressure of Normal and Hypophysectomized Rats. Am. J. Physiol. 139: 17, 1943.

The daily injection of stilbestrol into normal rats produces a gradual rise in systolic blood pressure, reaching hypertensive levels in many cases.

The systolic blood pressure of the untreated hypophysectomized rat decreased, on the average, 30 to 35 mm. below normal within ten days after hypophysectomy. Rats hypophysectomized for seven months had a blood pressure stabilized at this low level.

The injection of hypophysectomized rats with stilbestrol produced a fall in blood pressure below that of operated controls.

AUTHORS.

Book Review

IRRIGACION NORMAL DEL NODULO DE KEITH Y FLACK, TAWARA, HAZ DE HIS Y SUS RAMAS: By Dr. Eduardo F. Lascano, El Ateneo, Buenos Aires, 1942, 97 pages, 25 illustrations.

This monograph deals with the normal blood supply of the S-A node, the A-V node, and the His bundle and its branches. The coronary vessels were injected with gelatin, paraffin, or celloidin, with the addition of dyes or radiopaque substances. Dissection, roentgenograms, corrosion, and diaphanization were used.

The S-A node receives its blood supply from one auricular artery only. This may be one of the anterior, lateral, or posterior auricular ascending branches of the right and left circumflex arteries. There are, therefore, six different possibilities. This artery is larger than the others, and gives origin to a pericaval ring. The artery of the S-A node starts from this ring and runs along the sulcus terminalis.

The main artery of both the A-V node and the His bundle is the first posterior perforating artery, or the ramus septi fibrosi of Haas. It anastomoses with other vessels.

The right branch of the His bundle receives blood from three different groups of vessels:

1. An anastomotic plexus supplied by the ramus septi fibrosi, the ramus septi ventriculorum superior, the ramus cristae supraventricularis, and the first anterior perforating arteries.

2. A second plexus supplied by the ramus limbi dextri, the plexus of 1, and, also, collateral branches of both the anterior and posterior perforating arteries.

3. Nonspecified vessels of the myocardium.

The left branch of the His bundle receives blood from three different groups of vessels:

1. An anastomotic plexus supplied by terminal branches of the ramus septi fibrosi, the ramus cristae supraventricularis, the ramus limbi sinistri, and many other small arterioles.

2. Other anterior and posterior perforating arteries.

3. Nonspecific arteries of the extraseptal myocardium which anastomose freely with each other.

By means of various technical improvements, the author demonstrates that all arteries which supply blood to the node of Tawara, the His bundle, and the branches of the bundle anastomose with each other, as well as with nonspecific arteries of the myocardium. These arteries, therefore, should be considered only as main arteries, and not as terminal vessels.

Both the main arteries and the anastomoses run in the same direction as the excitation wave of the myocardium.

The study is well presented, and will be of interest to many students of cardiology. The photographs are remarkable.

ALDO LUISADA.

American Heart Association, Inc.

1790 BROADWAY AT 58TH STREET, NEW YORK, N. Y.

DR. ROY W. SCOTT
President

DR. HOWARD F. WEST
Vice-President

DR. GEORGE R. HERRMANN
Treasurer

DR. HOWARD B. SPRAGUE
Secretary

BOARD OF DIRECTORS

*DR. EDGAR V. ALLEN	Rochester, Minn.
DR. ARLIE R. BARNES	Rochester, Minn.
DR. CLARENCE DE LA CHAPELLE	New York City
DR. NORMAN E. FREEMAN	Philadelphia
*DR. TINSLEY R. HARRISON	Winston-Salem
DR. GEORGE R. HERRMANN	Galveston
DR. T. DUCKETT JONES	Boston
DR. LOUIS N. KATZ	Chicago
*DR. SAMUEL LEVINE	Boston
DR. GILBERT MARQUARDT	Chicago
*DR. H. M. MARVIN	New Haven
*DR. EDWIN P. MAYNARD, JR.	Brooklyn
*DR. THOMAS M. MCMILLAN	Philadelphia
DR. JONATHAN MEAKINS	Montreal
DR. E. STERLING NICHOL	Miami
DR. FRANKLIN R. NUZUM	Santa Barbara
DR. HAROLD E. B. PARDEE	New York City
DR. WILLIAM B. PORTER	Richmond, Va.
*DR. JOHN SAMPSON	San Francisco
*DR. ROY W. SCOTT	Cleveland
DR. FRED M. SMITH	Iowa City
DR. HOWARD B. SPRAGUE	Boston
DR. GEORGE F. STRONG	Vancouver, B. C., Can.
DR. WILLIAM D. STROUD	Philadelphia
DR. HARRY E. UNGERLEIDER	New York City
*DR. HOWARD F. WEST	Los Angeles
DR. PAUL D. WHITE	Boston
DR. FRANK N. WILSON	Ann Arbor
*DR. IRVING S. WRIGHT	New York City
DR. WALLACE M. YATER	Washington, D. C.

DR. H. M. MARVIN, *Acting Executive Secretary*
ANNA S. WRIGHT, *Office Secretary*
TELEPHONE, CIRCLE 5-8000

THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

Annual membership is $5.00. Journal membership at $11.00 includes a year's subscription to the AMERICAN HEART JOURNAL (January-December) and annual membership in the Association. The Journal alone is $10.00 per year.

The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

**Executive Committee.*